IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,474,787
Issued: October 2, 1984
To: Hugh Cairns and David Cox
For: **7,6 DIOXO-4H,6H-PYRANO[3,2-G]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF**
Expiration Date: October 2, 2001

LETTER

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Enclosed are the following papers re the above:

1. Application for Extension of Patent Term of U.S. Patent No. 4,474,787 under 35 U.S.C. §156 (in duplicate);

2. Power of Attorney; and

3. Our check in the amount of $1,000.00.

If for any reason the above-mentioned check is not attached or enclosed herewith, or is for an incorrect amount, or is irregular or defective, please charge any additional fees, or the entire fee, or credit overpayment to Deposit Account No. 13-2855. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BICKNELL

By: Basil P. Mann

Basil P. Mann
Registration No. 18,464
A Member of the Firm
Two First National Plaza
Chicago, Illinois 60603
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Chicago, Illinois

February 22, 1993

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,474,787
Issued: October 2, 1984
To: Hugh Cairns and David Cox
For: **7,6 DIOXO-4H,6H-PYRANO[3,2-g]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF**
Expiration Date: October 2, 2001

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Hon. Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Applicant, Fisons plc (formerly Fisons Limited), represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,474,787, granted to Hugh Cairns and David Cox on October 2, 1987 for **7,6 DIOXO-4H,6H-PYRANO[3,2-g]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF** by virtue of an assignment recorded October 26, 1978, Reel 3588, Frame 809.

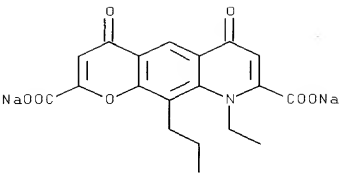
In support of this application, applicant provides the requisite information following the sections of 37 CFR §1.740.

1.740(a)(1): APPROVED PRODUCT

Trade and generic names: TILADE® (nedocromil sodium inhalation aerosol).

Description (product): A pressurized metered-dose aerosol suspension for oral inhalation containing micronized nedocromil sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each actuation delivers from the mouthpiece 1.75 mg nedocromil sodium. Each 16.2 g canister provides for at least 112 metered inhalations.

Active ingredient: The structural formula of nedocromil sodium is



Chemical name: **[patent]** 4,6-dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline dicarboxylic acid, disodium salt.

[product labelling] 4H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt.

Both compound names are identified (in the acid form) by Chemical Abstracts under Registry Number 69049-73-6 as shown in Appendix 1.

The synthesis of nedocromil sodium as described in Example 2 of U.S. Patent 4,474,787 is given in Appendix 2. The steps marked with letters refer to the steps in the patent example. It is apparent that nothing other than nedocromil sodium could be produced from this synthesis route.

The difference in the names of the active ingredient arises from the fact that the structure was described in the patent as a 4H,6H-pyranoquinoline numbered counterclockwise starting with the ring nitrogen whereas it is now (under IUPAC nomenclature) described as a 4H-pyranodihydroquinoline, numbered clockwise starting with the ring oxygen. Both names, however, identify the same compound.

Empirical formula (calculated as anhydrous): $C_{19}H_{15}NNa_2O_7$.

Molecular weight (calculated as anhydrous): 415.3.

Description (active ingredient): a yellow hydrated powder, soluble in water.

1.740(a)(2): Section 505(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(a).

1.740(a)(3): **Date of approval letter giving permission for commercial marketing or use:** 30 December 1992.

1.740(a)(4): The only active ingredient in the approved product, nedocromil sodium, has not previously been approved for commercial marketing or use pursuant to the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

1.740(a)(5): This application is being submitted within the sixty (60) day period permitted for submission pursuant to 37 CFR §1.720(f). The last day on which the application can be submitted is 28 February 1993.

1.740(a)(6): **Patent number**: 4,474,787

Inventors: Hugh Cairns and David Cox, both of Loughborough, England.

Date of issue: 2 October 1984

Date of expiration: 2 October 2001

1.740(a)(7): A copy of U.S. patent 4,474,787 is included in attached Appendix 3.

1.740(a)(8): A copy of a certificate of correction issued April 9, 1985 is included in Appendix 4. Also enclosed in Appendix 4 is a copy of a recently filed request for a Certificate of Correction to correct an obvious printing error in the claims of the patent.

Copies of two receipts for maintenance fee payments issued on the patent are attached in Appendix 5.

1.740(a)(9): The patent claims the approved product. Claims 1, 2, 3, 4, 5, 6, 8, 9, and 11 of the patent read on the approved product as follows:

(a) Claim 1 defines the generic formula encompassing nedocromil, the parent acid of nedocromil sodium. The claim reads on nedocromil when R_5 represents hydrogen, R_6 and R_7 together represent a chain -COCH=C(COOH)-O-, R_8 represents an alkyl group containing three carbon atoms and R_g represents an alkyl group containing two carbon atoms. Nedocromil sodium is covered by this claim, being a pharmaceutically acceptable salt of nedocromil.

(b) Claim 2 further defines the generic formula encompassing nedocromil sodium. R_8 and R_g, being alkyl, contain three and two carbon atoms respectively.

(c) Claim 3 further defines the generic formula encompassing nedocromil sodium as the

(d) Claim 4 further defines the generic formula encompassing nedocromil sodium as R_5 and R_8 are hydrogen and propyl respectively.

(e) Claim 5 further defines the generic formula encompassing nedocromil sodium as R_g represents ethyl.

(f) Claim 6 explicitly claims nedocromil and pharmaceutically acceptable salts such as nedocromil sodium. See entry under 1.740(a)(1) above.

(g) Claim 8 claims pharmaceutical compositions including nedocromil sodium in combination with a pharmaceutically acceptable adjuvant, diluent or carrier in the treatment of a condition involving an antibody antigen reaction or a reflex pathway. This covers **TILADE** which is indicated for treatment of bronchial asthma, an allergic condition of the airways, and which comprises nedocromil sodium formulated with a surfactant and an aerosol propellant.

(h) Claim 9 covers the approved product, which contains approximately 1.4% w/w of active ingredient.

(i) Claim 11 claims the method of treatment for which **TILADE** is indicated.

1.740(a)(10)(i): **Effective date of IND application**: 6 March 1983.

IND number: 21,544.

NDA submission: 27 February 1987.

NDA approval: 30 December 1992.

NDA number: 19-660

1.740(a)(11): A description of the significant activities (with dates) with respect to the approved product during the applicable regulatory period is given in Appendix 6.

1.740(a)(12): In the opinion of applicant, the patent is entitled to an extension for a period of five years.

The extension has been calculated from the following dates:

IND Effective Date: 6 March 1983
Date of Patent Grant: 2 October 1984
Date of NDA Submission: 27 February 1987
Date of NDA Approval: 30 December 1992

Under 35 U.S.C. §156(c), the period of entitlement is calculated to be about seven years, including one-half the period from 2 October 1984 to 27 February 1987 (35 U.S.C. §156(g)(1)(B)(i)) and the entire period between 27 February 1987 and 30 December 1992 (35 U.S.C. §156(g)(1)(B)(ii)).

However, under 35 U.S.C. §156(g)(6)(A), the maximum period of extension is five years, since the patent issued after 24 September 1984.

The period remaining in the original term of the patent after NDA approval of the product (from 30 December 1992 to 2 October 2001) is approximately eight years, nine months. Accordingly, an extension of five years in the term of the patent would not result in a total term exceeding 14 years, as specified in 35 U.S.C. §156(c)(3).

1.740(a)(13): Applicant acknowledges its duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services all information which it believes is material to the determination of entitlement to the extension sought.

1.740(a)(14): The prescribed fee of $1,000.00 is enclosed herewith. Also enclosed in duplicate is an authorization to charge Deposit Account No. 13-2855 for any deficiency.

1.740(a)(15): All correspondence relating to the application should be sent to applicant's attorney:

Basil P Mann, Esq.
Marshall O'Toole, Gerstein,
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
Telephone: (312) 474-6300
Facsimile No.: (312) 474-0448

1.740(a)(16): A certified copy of the application papers is enclosed in Appendix 7.

1.740(a)(17): DECLARATION

The undersigned attorney for applicant declares that he is authorized to practice before the Patent and Trademark Office (Registration No. 18,464) and that he has general authority to act on behalf of applicant, with respect to this Application for Extension of Patent Term;

That he has reviewed and understands the contents of this Application for Extension of Patent Term of U.S. Patent No. 4,474,787, comprising the foregoing 7 pages and appendices 1-7;

That he believes the patent is subject to extension pursuant to 37 CFR §1.710;

That he believes an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

That he believes the patent for which the extension is sought meets the conditions for extension of the term of a patent as set forth in 37 CFR §1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

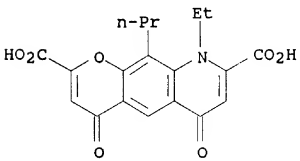
Basil P. Mann
Registration No. 18,464

Date: Feb. 19, 1993
42422

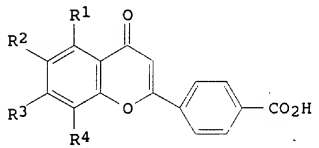
APPENDIX 1

Chemical Abstracts entries for nedocromil
(Registry Number 69049-73-6)

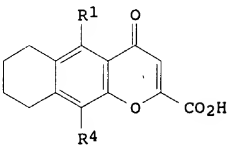
L1 ANSWER 1 OF 1 COPYRIGHT 1993 ACS
RN **69049-73-6** REGISTRY
CN 4H-Pyrano[3,2-g]quinoline-2,8-dicarboxylic acid,
9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Nedocromil
FS 3D CONCORD
MF C19 H17 N O7
CI COM
LC BEILSTEIN, BIOSIS, CA, CAPREVIEWS, CIN, EMBASE, MEDLINE, PHAR, WHO



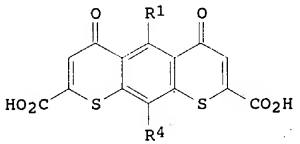
L2 ANSWER 105 OF 108 COPYRIGHT 1993 ACS
AN CA98(17):137619b
TI Benzopyran derivatives as therapeutic agents
CS Fisons Ltd.
LO UK
SO Jpn. Kokai Tokkyo Koho, 7 pp.
PI JP 58004722 A2 11 Jan 1983 Showa
AI JP 82-107709 24 Jun 1982
PRAI GB 81-19624 25 Jun 1981
IC A61K031-35; A61K031-38; A61K031-47
PY 1983
LA Japan
GI



I



II



III

AB 6-methylamino-4-oxo-10-propyl-4H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid [85197-10-0], 1-ethyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid [69049-73-6], I, II, or III (R1 = H, OH, alkyl, etc.; R2 and R3 = H or alkyl; R4 = H, alkyl, or hydroxyalkyl) are effective in treating diabetes, neuropathy, and eye and renal diseases, etc. Oral administration of these drugs to rats with streptozotocin-induced diabetes showed therapeutic effects by inhibiting the accumulation of sorbitol in sciatic nerves.

KW benzopyran deriv eye kidney disease; diabetes benzopyran deriv; nerve disease benzopyran deriv

IT Diabetes mellitus
(neuropathy in, treatment of, with benzopyrans)

IT Eye, disease or disorder
Nerve, disease or disorder
Kidney, disease or disorder
(treatment of, with benzopyrans)

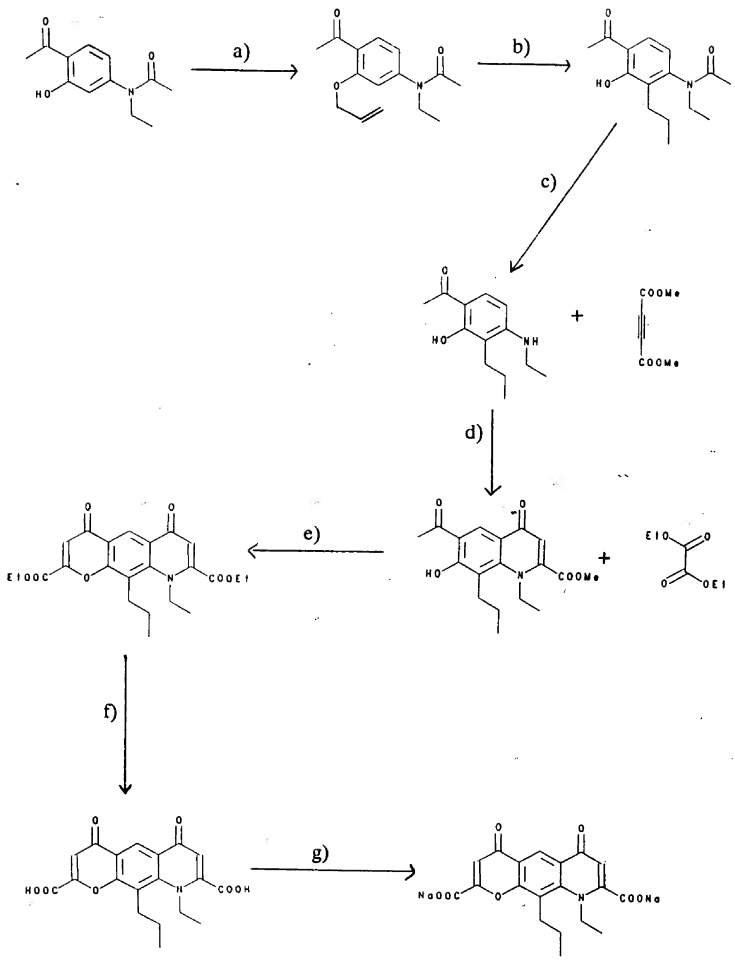
IT 254-04-6D, derivs.
(pharmaceutical contg.)

IT 39849-03-1 60401-04-9 60401-24-3 60401-91-4 **69049-73-6**
85197-10-0 85197-11-1
(pharmaceuticals contg.)

APPENDIX 2

Synthesis of nedocromil sodium

Synthesis of nedocromil sodium
Example 2



APPENDIX 3

U.S. Patent No. 4,474,787

United States Patent [19]

Cairns et al.

[11] **Patent Number: 4,474,787**

[45] **Date of Patent: Oct. 2, 1984**

[54] **7,6 DIOXO-4H,6H-PYRANO[3,2-g]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF**

[75] Inventors: **Hugh Cairns; David Cox**, both of Loughborough, England

[73] Assignee: **Fisons Limited**, England

[21] Appl. No.: **344,982**

[22] Filed: **Feb. 2, 1982**

Related U.S. Application Data

[63] Continuation of Ser. No. 946,492, Sep. 28, 1978, abandoned, which is a continuation-in-part of Ser. No. 897,416, Apr. 18, 1978, abandoned.

[30] **Foreign Application Priority Data**

May 4, 1977 [GB] United Kingdom 18597/77
Nov. 4, 1977 [GB] United Kingdom 48565/77
Apr. 25, 1978 [GB] United Kingdom 16168/78

[51] **Int. Cl.**[3] **A61K 31/47**; C07D 491/04

[52] **U.S. Cl.** **424/258**; 546/89; 546/92

[58] **Field of Search** 546/89, 92; 424/258

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,773,769 11/1973 Albrecht et al. 546/89
4,117,134 9/1978 Connor et al. 546/92

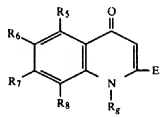
FOREIGN PATENT DOCUMENTS

073427 3/1975 Japan 546/89

Primary Examiner—Glennon H. Hollrah
Assistant Examiner—D. B. Springer
Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein, Murray & Bicknell

[57] **ABSTRACT**

There are described compounds of formula *i*



I

in which an adjacent pair of R_5, R_6, R_7 and R_8 form a chain —COCH=CE--O—, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and

E is —COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable derivatives thereof.

There are also described processes for making the compounds and pharmaceutical, e.g. anti-allergic, compositions containing the compounds.

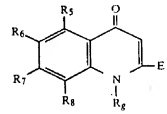
11 Claims, No Drawings

7,6 DIOXO-4H,6H-PYRANO[3,2-G]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF

This is a continuation of application Ser. No. 946,492, filed Sept. 28, 1978 abandoned which is a CIP of Ser. No. 897,416 filed Apr. 18, 1978 abandoned.

This invention relates to new pyranoquinolinone derivatives, compositions containing them and methods for their preparation.

According to our invention we provide compounds of formula I,



I

in which an adjacent pair of R_5, R_6, R_7 and R_8 form a chain —COCH=CE—O—, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

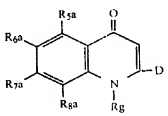
Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and

E is —COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl)carboxamido group,

and pharmaceutically acceptable derivatives thereof.

According to our invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable derivative thereof, which comprises,

(a) producing a compound of formula I in which E is —COOH by selectively hydrolysing or oxidising a compound of formula II,



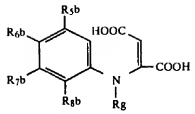
II

in which Rg is as defined above,

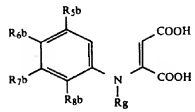
R_{5a}, R_{6a}, R_{7a} and R_{8a} have the same significances as R_5, R_6, R_7 and R_8 above, save than an adjacent pair of R_{5a}, R_{6a}, R_{7a} and R_{8a} may represent a chain of formula —COCH=C(D_1)O—, and

one or both of D and D_1 represents a group hydrolysable or oxidisable to a —COOH group, and the other may represent a —COOH group,

(b) producing a compound of formula I in which E is —COOH by cyclising a compound of formula III or IV,



III



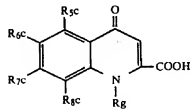
IV

or an ester of either thereof,

in which Rg is as defined above,

R_{5b}, R_{6b}, R_{7b} and R_{8b} have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_{5b}, R_{6b}, R_{7b} and R_{8b} may represent the pair of groups —H and —O—C(COOH)=CH—COOH,

(c) producing a compound of formula I in which E is —COOH by cyclising a compound of formula V,



V

or an ester thereof,

in which Rg is as defined above,

R_{5c}, R_{6c}, R_{7c} and R_{8c} have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_{5c}, R_{6c}, R_{7c} and R_{8c}, instead of forming a chain —COCH=C(COOH)—O—, represent the pairs of groups:

(i) $-COCH_2CO-COR''$ or $-COCH=C(COOH-)-NL_1L_2$, or a suitable derivative thereof; and —OM or a halogen atom, or

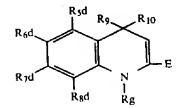
(ii) —H and —O—C(COR")=CH—COR"

R" represents —OM, or a group which is hydrolysable thereto,

L_1 and L_2 which may be the same or different are each hydrogen, aryl or alkyl, or together form a saturated or unsaturated alkylene chain, and

M represents hydrogen or an alkali metal, and if necessary or desired hydrolysing the group —COR", to a group —COOM,

(d) conversion of a compound of formula VI,



VI

or an ester thereof,

in which Rg and E are as defined above,

R_{5d}, R_{6d}, R_{7d} and R_{8d} have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair

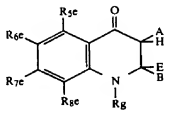
of R_{5d}, R_{6d}, R_{7d} and R_{8d} may represent the chain $-C(R_9R_{10})=CE-O-$,

at least one of the pairs of groups R_9 and R_{10} together form a $=S$ or together form an $-S(CH_2)_nS-$ chain in which n is 2 or 3, and the other pair R_9, R_{10} may represent $=O$,

to a corresponding compound of formula I,

(e) selectively removing the groups A and B from a compound of formula VII,

VII



or an ester thereof,

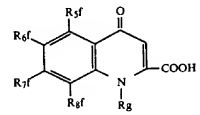
in which Rg and E are as defined above,

R_{5e}, R_{6e}, R_{7e} and R_{8e} have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_{5e}, R_{6e}, R_{7e} and R_{8e} may represent a chain $-COCHA-CBE-O-$,

in at least one of the pairs of groups A and B both A and B are hydrogen, or one of A and B is hydrogen and the other is halogen or hydroxy, and the other pair A, B may together form a double bond,

(f) producing a compound of formula I in which E is $-COOH$ by cyclising a compound of formula VIII,

VIII



or an ester thereof,

in which Rg is as defined above, R_{5f}, R_{6f}, R_{7f} and R_{8f} have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_{5f}, R_{6f}, R_{7f} and R_{8f}, instead of forming a chain $-COCH=C(COOH)-O-$, represent the pair of groups $-COCH(SOR_{10})-CH(CH)-COOR''$ and $-OM$,

R'' and M are as defined above, and

R_{10} represents an alkyl C 1 to 10 group,

(g) producing a compound of formula I in which E is a 5-tetrazolyl group by reacting a corresponding compound of formula I in which E is $-CN$, with an azide in a solvent which is inert under the reaction conditions, or

(h) producing a compound of formula I in which E is an (N-tetrazol-5-yl)carboxamido group by reacting a corresponding compound of formula I in which E is $-COOH$, or an acid halide, ester or mixed anhydride thereof,

with 5-aminotetrazole,

and if necessary or desired hydrolysing the ester of the compound of formula I and/or converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

In process (a) the group D may be, for example an ester, acid halide, amide or a nitrile group, which may be hydrolysed to a $-COOH$ group. The hydrolysis may be carried out using conventional techniques, for example under mildly basic conditions, e.g. using sodium carbonate, sodium hydroxide, sodium bicarbonate, or under acidic conditions, e.g. a mixture of aqueous dioxan and hydrochloric acid, or hydrogen bromide in acetic acid. The hydrolysis may be carried out at a temperature of from about 25° to 120° C. depending on the compounds used. Alternatively the group D may be an alkyl, e.g. a lower alkyl such as methyl, a hydroxymethyl, an aralkenyl, e.g. styryl, an acyl, e.g. a lower alkanoyl such as acetyl, or a formyl group. The oxidation may be carried out using conventional techniques which do not otherwise modify the molecule to such an extent that the yield of the desired product is uneconomical, for example an alkyl or a hydroxymethyl group may be oxidised using selenium dioxide, e.g. under reflux in aqueous dioxan; or chromic acid, e.g. under reflux in aqueous acetic acid. Aralkenyl groups may be oxidised using, for example neutral or alkaline potassium permanganate in aqueous ethanol, and acyl groups may be oxidised using, for example chromic acid or an aqueous hypochlorite, e.g. sodium hypochlorite. The formyl group may be oxidised using, for example chromic acid or silver oxide.

In process (b) the cyclisation may be carried out by treating the compound of formula III or IV, with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, sulphuric or polyphosphoric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of from about 25° to 150°, and preferably from 75° to 150° C. We have found that isomerisation of the maleic acid derivative of formula IV to the corresponding fumaric acid derivative of formula III takes place when polyphosphoric acid is used to cyclise these compounds to a compound of formula I, thus enabling a satisfactory yield of the compound of formula I to be obtained from a *prima facie* unsatisfactory mixture of compounds of formulae III and IV. Compounds of formula III may also be cyclised by subjecting the compound to an elevated temperature, e.g. of from 200° to 250° C., optionally in the presence of a high boiling solvent which is inert under the reaction conditions, e.g. diphenyl ether.

When one of the groups is —OM the cyclisation of process (c)(i) may be carried out by heating, or under basic or neutral conditions. It is however preferred to carry out the cyclisation in the presence of an acid, e.g. hydrochloric acid, and in a solvent which is inert under the reaction conditions, e.g. ethanol. The reaction may be carried out at from about 20° to 150° C. The group $-COR''$ is preferably an ester group, e.g. R'' may be a lower alkoxy group. When one of the groups is $-COCH=C(COOH)-NL_1L_2$ the derivative of the $-COOH$ group may be a group $-CONL_1L_2$ in which L_1 and L_2 are as defined above. It is preferred that L_1 and L_2 are hydrogen, phenyl, alkyl C 1 to 6 or together form a 4 or 5 membered alkylene chain, e.g. together with the nitrogen atom form a piperidine ring. When one of the groups is halogen the cyclisation may be carried out in a solvent which is inert under the reaction conditions, preferably a high boiling polar solvent, e.g. pyridine, dimethylformamide or hexamethylphosphoramide. The reaction is preferably carried out with the aid of a strong base, for example an alkali metal hydride, e.g. sodium hydride. The reaction is preferably carried out at a temperature of from about 80° to 200° C., in the absence of free oxygen, e.g. under an inert atmosphere such as nitrogen.

The cyclisation of process (c)(ii) may be carried out by treating the compound of formula V with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, polyphosphoric or sulphuric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of from 0° to 100° C. Alternatively cyclisation may be achieved by converting the free carboxy groups of the compound of formula V to acyl halide groups and subjecting the resulting acyl halide to an intramolecular Friedel-Crafts reaction.

In processes (d), when R_9 and R_{10} together form a chain $-S-(CH_2)_n-S-$, the conversion may comprise oxidative hydrolysis and may be carried out in an aqueous polar organic solvent, for example aqueous ethanol, acetone or tetrahydrofuran. The oxidative hydrolysis may be carried out in the presence of an oxidising agent, for example mercuric chloride, an N-halosuccinimide such as N-bromo- or N-chloro-succinimide, a per-acid such as periodic acid; or p-toluenesulphonchloramide or a salt thereof. When mercuric chloride is used the reaction may be carried out in the presence of a base, e.g. mercuric oxide, cadmium carbonate or calcium carbonate. N-halosuccinimides may be used alone or in the presence of a silver salt, e.g. silver perchlorate, or silver nitrate. The reaction may conveniently be carried out at a temperature of from about 15° to 100° C.

When R_9 and R_{10} together form a $=S$ group the conversion may comprise (oxidative) hydrolysis and may be carried out in the presence of a heavy metal compound, e.g. a compound of group Ib, IIb or IIIb of the Periodic Table of Mendeleef, as catalyst. Suitable compounds include mercury, thallium and silver compounds, e.g. mercury (II) acetate or chloride, thallium (III) trifluoroacetate, or silver oxide. The reaction may be carried out in the presence of water an an organic solvent system such as acetone-acetic acid, alkanols, tetrahydrofuran/methanol, or tetrahydrofuran. Alternatively the reaction may be carried out by alkylation followed by hydrolysis. In such cases the reaction may be effected by (i) an alkyl halide or sulphonate (e.g. methyl iodide), in a moist solvent, e.g. acetone, (II) an alkylfluorosulphonate and water in sulphur dioxide, or (iii) a trialkyl oxonium fluoroborate followed by aqueous sodium hydroxide.

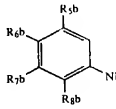
When both A and B are hydrogen process (e) is a dehydrogenation and may be carried out by oxidation using a mild oxidising agent, for example selenium dioxide, palladium black, chloranil, lead tetraacetate or triphenyl methyl perchlorate. Alternatively the dehydrogenation of a compound of formula VII in which both A and B are hydrogen may be carried out indirectly by halogenation followed by dehydrohalogenation, e.g. by treatment with N-bromosuccinimide or pyridinium bromide perbromide to yield a compound of formula VII in which A is halogen and B is hydrogen, which is subsequently dehydrobrominated. When one of A and B is hydroxy the dehydration may be catalysed by an acid, e.g. sulphuric or oxalic acid; a base, e.g. potassium hydroxide; or a salt, e.g. potassium hydrogen sulphate; or N-bromosuccinimide. The reaction may be carried out in a solvent which is inert under the reaction conditions, e.g. a halogenated hydrocarbon, xylene, or glacial acetic acid. The reaction may be carried out at an elevated temperature, e.g. from 20° to 150° C.

The cyclisation of process (f) may be carried out in a solvent which is inert under the reaction conditions, e.g. diethyl ether or benzene. The reaction may also, if desired, be carried out in the presence of a Lewis acid, e.g. boron trifluoride. The reaction is preferably carried out at a temperature of from 10° to 120° C. in presence of an organic base, e.g. piperidene.

Suitable solvents which are inert under the reaction conditions of process (g) include those in which both the reagents are soluble, e.g. N,N-dimethylformamide. Other solvents which may be mentioned include dimethylsulphoxide, tetrahydrofuran, diethyl glycol and ethyl methyl glycol. The reaction is preferably carried out at a temperature of from about 20° to 130° C. for from about 1 to 20 hours. The azide used in the reaction is preferably ammonium or an alkali metal azide, e.g. sodium or lithium azide, but other azides, e.g. aluminium azide or the azides of nitrogen containing bases, e.g. mono-, di-, tri-, and tetra- methyl- ammonium, anilinium, morpholinium and piperidinium azides, may also be used if desired. Where an azide other than that of an alkali metal is used this azide may be prepared in the reaction mixture by double decomposition. The reaction may, if desired, be carried out in the presence of an electron acceptor, e.g. aluminium chloride, boron trifluoride, ethyl sulphonic acid or benzene sulphuric acid. As an alternative to the reaction conditions set out above, the reaction may be carried out using hydrazoic acid (hydrogen azide) at a temperature of from about 20° to 150° C. in a suitable solvent, under greater than atmospheric pressure. When an azide other than hydrazoic acid is used, e.g. sodium azide, the product of the reaction will be the corresponding tetrazole salt. This salt may readily be converted to the free acid by treatment with strong acid, e.g. hydrochloric acid.

In process (h) the anhydride is preferably a mixed anhydride of such a type that it will cleave preferentially, to give the desired chromone carboxamidotetrazole, as the major product when reacted with the 5-aminotetrazole. Examples of suitable acids from which the mixed anhydride may be derived are sulphonic acids e.g. benzene sulphonic acid, sterically hindered carboxylic acids, e.g. pivalic, isovaleric, diethylacetic or triphenylacetic acid, and alkoxy formic acids, e.g. a lower alkoxy formic acid such as ethoxy or isobutoxy formic acid. When an acid halide is used it may conveniently be an acid chloride. The reaction is preferably carried out under anhydrous conditions in a solvent which will not react with either the 5-aminotetrazole or the mixed anhydride or acid halide, e.g. pyridine or dimethylformamide. However when the reaction is carried out in a non-basic solvent, e.g. dimethylformamide, an adequate proportion of an acid acceptor, e.g. triethylamine, should also preferably be present. The reaction is preferably carried out at a temperature of from about $-15°$ to $+20°$ C. When an ester is used we prefer to use a lower alkoxy ester and to carry out the reaction in a solvent which is inert under the reaction conditions, e.g. glacial acetic acid, at a temperature of from about 100° to 150° C. When a compound of formula I in which E is —COOH is used as starting material the reaction may be carried out by heating the compound of formula I and the 5-aminotetrazole in a solvent which is inert under the reaction conditions, e.g. dimethylacetamide, at a temperature of from 100° to 200° C. Alternatively the reaction may be carried out in the presence of a condensation agent, e.g. N,N'-carbonyl-diimidazole or dicyclohexyl carbodiimide, in an aprotic solvent, e.g. dimethylformamide, at a temperature of from about 10° to 40° C.

The starting materials for process (b) may be made by reacting a compound of formula IX,

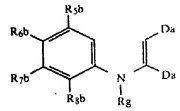


IX

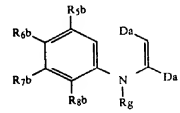
in which Rg, R5b, R6b, R7b and R8b are as defined above, with a compound of formula X,

Da—C≡C—Da X

in which Da is an ester group,
to produce a mixture of compounds of formulae XI and XII,



XI



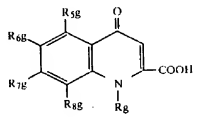
XII

in which Rg, Da, R5b, R6b, R7b and R8b are as defined above.

The compounds of formula XI and XII may be hydrolysed to give compounds of formulae IV and III. Alternatively the groups Da in the compounds of formulae XI and XII may be converted using conventional techniques known per se, to other groups D and the resulting comounds cyclised, using the same conditions as for process (b) above, to yield a compound of formula II. As a further and preferred alternative the compounds of formula XI and XII may by cyclised, using the same conditions as for process (b) above, to give a compound of formula II in which D is an ester group, and the resulting compound of formula II is used itself in process (a), or the D group converted to another group D, e.g. an acid halide, amide or nitrile group, using techniques known per se.

The fumarate isomer of formula XII (or the corresponding compound in which Da has been converted to D) is the only isomer which can cyclise to give the required compounds of formula II. The proportion of the two isomers may be readily determined by nuclear magnetic resonnance spectroscopy and we have found that, in general, the desired fumaric acid derivative is only a minor proportion of the mixture of isomers obtained from the reaction.

The compounds of formula V, in which an adjacent pair of R5c, R6c, R7c and R8c represent the groups —$COCH_2COCOR''$ and —OM or halogen, may be made by reacting a compound of formula XIII,



XIII

or an ester thereof,
in which Rg is as defined above,
and R5g, R6g, R7g and R8g have the same significances as R5, R6, R7 and R8 above, save that an adjacent pair of R5g, R6g, R7g and R8g, instead of forming a —COCH=CH(COOH)—O— chain, represent the groups —$COCH_3$ and —OM or halogen, in which M is as defined above,
with a compound of formula XIV,

R'CZ—CZR'' XIV

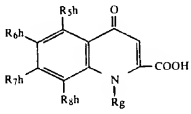
in which R'' is as defined above,
R' is a suitable leaving group, e.g. an alkoxy, halo, amino, alkylamino, substituted amino (e.g. an arylsulphonylamino group) or substituted alkylamino group, reactive with the carbanion of the —$COCH_3$ group of the compound of formula XIII, and
each Z is a carbonyl oxygen atom, or one Z may represent two halogen atoms and the other a carbonyl oxygen atom,
and if necessary hydrolysing the resulting compound to a compound of formula V. The preferred comounds of formula XIV are dialkyl oxalates, e.g. diethyl oxalate.

Compounds of formula V bearing a —COCH=C(COOH)—NL_1L_2 group, or a derivative thereof, may be made from known compounds in one or more steps using processes known per se.

The compounds of formula II may be made as described above or by a process analogous to process (c)(i).

Alternatively the compounds of formula II may, for example in the case of the acid halide, the amide and the nitrile, be made from comounds of formula I using conventional techniques, e.g. reaction of an ester of the compound of formula I with ammonia to produce the amide, followed by dehydration of the amide to form the nitrile.

The compounds of formula V carrying substituents —H and —O—C(COR'')=CH—COR'' may be made by reacting a compound of formula XV,

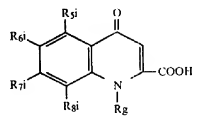


XV

or an ester thereof,
in which Rg is as defined above, and R5h, R6h, R7h and R8h have the same significances as R5, R6, R7 and R8 above, save that an adjacent pair of R5h, R6h, R7h and R8h, instead of forming a —COCH=C(COOH)—O— chain, represent the groups —H and —OH.

with a dialkyl acetylene dicarboxylate, in conventional manner, followed if necessary by hydrolysis of the reaction product.

Compounds of formula VIII may be made by reacting a compound of formula XVI,



XVI

or an ester thereof,

in which Rg is as defined above,

R_5i, R_6i, R_7i and R_8i have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5i, R_6i, R_7i and R_8i, instead of forming a chain —COCH=C(COOH)—O—, represent the pair of groups —OH and —COO—Alkyl,

with a methyl alkyl sulphoxide anion, e.g. the anion of dimethyl sulphoxide,

and reacting the resulting o-hydroxy-2-alkylsulphinyl compound with glyoxalic acid or an ester thereof.

The compounds of formula I in which E is —CN may be made by dehydrating the corresponding pyranoquinoline amide using, for example, phosphorus oxychloride, as dehydrating agent. The reaction is preferably carried out using at least one molar equivalent of dehydrating agent per mole of the pyranoquinolinone amide. Where the dehydrating agent reacts with one of R_5, R_6, R_7 or R_8 (e.g. a substituent comprising an —CH group) sufficient dehydrating agent should be used to satisfy the side reaction as well as the main reaction. The reaction may, if desired, be carried out in the presence of an acid binding agent, e.g. triethylamine. The reaction may be carried out in the presence of a solvent, e.g. N,N-dimethylformamide, dimethyl sulphoxide, pyridine, benzene or hexamethyl phosphoramide, or an excess of the dehydrating agent may be used as the reaction medium. The reaction may be carried out at a temperature of from about 0° to 200° C. depending on the dehydrating agent used. When phosphorus oxychloride is used a temperature of from 0° to 100° C. is preferred.

The chromone amide starting materials may be made by reacting a corresponding pyranoquinolinone ester with ammonia, using techniques conventional in the production of amides from esters, e.g. using an alkanol as solvent at a temperature of 0° to 120° C.

Compounds of formulae VI, VII, IX, XIII, XIV, XV and XVI are either known or may be made from known compounds using conventional techniques known per se.

The processes as described above may produce the compound of formula I or a derivative thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

The compounds of formula I and the intermediates therefore may be isolated from their reaction mixtures using conventional techniques.

Pharmaceutically acceptable derivatives of the compounds of formula I include pharmaceutically acceptable salts, and when E is a —COOH group, esters and amides of the 2-carboxylic acid group. Suitable salts include ammonium, alkali metal (e.g sodium, potassium and lithium) and alkaline earth metal (e.g. calcium or magnesium) salts, and salts with suitable organic bases, e.g. salts with hydroxylamine, lower alkylamines such as methylamine or ethylamine, with substituted lower alkylamines, e.g hydroxy substituted alkylamines such as tris(hydroxymethyl)methylamine, or with simple monocyclic nitrogen heterocyclic compounds, e.g piperidine or morpholine. Suitable esters include simple lower alkyl esters, e.g the ethyl ester, esters derived from alcohols containing basic groups, e.g di-lower alkyl amino substituted alkanols such as the β-(diethylamino)-ethyl ester, and acyloxy alkyl esters, e.g a lower acyloxy-lower alkyl ester such as the pivaloyloxymethyl ester, or a bis-ester derived from a di-hydroxy compound, e.g a di(hydroxy-lower alkyl)ether, e.g the bis-2-oxapropan-1,3-diyl ester. The pharmaceutically acceptable acid addition salts of the basic esters, and also of those compounds in which one of R_5, R_6, R_7 and R_8 is a group $—NR_1R_2$, e.g the hydrochloride, the hydrobromide, the oxalate, the maleate or the fumarate salts, may also be used. The esters may be made by conventional techniques, e.g esterification or transesterification. The amides may be, for example, unsubstituted or mono- or di- C 1 to 6 alkyl amides and may be made by conventional techniques, e.g reaction of an ester of the corresponding acid with ammonia or an appropriate amine.

The compounds of formula I and pharmaceutically acceptable derivatives thereof are useful because they possess pharmacological activity in animals; in particular they are useful because they inhibit the release and/or action of pharmacological mediators which result from the in vivo combination of certain types of antibody and specific antigen, e.g the combination of reaginic antibody with specific antigen (see Example 27 of British Patent Specification No. 1,292,601). The new compounds have also been found to interfere with reflex pathways in experimental animals and man and in particular those reflexes associated with lung function. In man, both subjective and objective changes which result from the inhalation of specific antigen by sensitised subjects are inhibited by prior administration of the new compounds. Thus the new compounds are indicated for use in the treatment of reversable airway obstruction and/or to prevent the secretion of excess mucous. The new compounds are thus indicated for the treatment of allergic asthma, so-called 'intrinsic' asthma (in which no sensitivity to extrinsic antigen can be demonstrated), bronchitis, coughs and the nasal and bronchial obstructions associated with the common colds. The new compounds may also be of value in the treatment of other conditions in which antigen-antibody reactions or excess mucous secretion are responsible for, or are an adjunct to, disease, for example, hay fever; certain eye conditions, e.g trachoma; alimentary allergy, e.g urticaria and atopic eczema; and gastrointestinal conditions, for example gastrointestinal allergy, especially in children, e.g milk allergy, or ulcerative colitis.

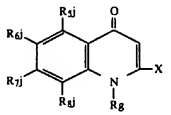
For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 0.001 to 50 mg per kg of animal body weight in the test set out in Example 27 of British Patent Specification No. 1,292,601. For man the indicated total daily dosage is in the range of from 0.01 mg to 1,000 mg

preferably from 0.01 mg to 200 mg and more preferably from 1 mg to 60 mg, which may be administered in divided doses from 1 to 6 times a day or in sustained release form. Thus unit dosage forms suitable for administration (by inhalation or oesophagally) comprise from 0.01 mg to 50 mg, preferably 0.01 mg to 20 mg and more preferably from 0.01 mg to 10 mg of the compound preferably admixed with a solid or liquid pharmaceutically acceptable diluent, carrier or adjuvant.

The compounds of formula I, and pharmaceutically acceptable derivatives thereof, have the advantage that they are more efficacious in certain pharmacological models, or are longer acting than compounds of similar structure to the compounds of formula I. Furthermore the compounds of formula I, and pharmaceutically acceptable derivatives thereof, are advantageous in that they are more efficaceous in interfering with reflex pathways and in inhibiting the secretion of mucous than are compounds of similar structure to the compounds of formula I.

We prefer each of R_g, R_5, R_6, R_7 and R_8, when they contain carbon, to contain up to 8, and preferably up to 4 carbon atoms. Specifically we prefer R_5, R_6, R_7 and R_8 to be selected from hydrogen, methoxy, propyl, allyl, methyl, ethyl, chlorine, bromine and hydroxy. The —COCH=CE—O— chain may be bonded to the benzene ring in any sense and in any of the adjacent positions R_5, R_6, R_7, R_8. However, we prefer the chain to be bonded in the positions R_6 and R_7 the —O— part of the chain being in position R_7. We also prefer the group E to be a —COOH group.

According to the invention there is also provided a process for the production of a pharmaceutically acceptable salt of a compound of formula I, which comprises treating a compound of formula Ic,



Ic

in which Rg is as defined above,

R_5j, R_6j, R_7j and R_8j have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5j, R_6j, R_7j and R_8j may form a chain —O—C(X)=CHCO—, and

X is a 5-tetrazolyl group, an (N-tetrazol-5-yl)carboxamido group, a carboxylic acid group (or an ester thereof, or another salt thereof), a nitrile group, an acid halide group or an amide group,

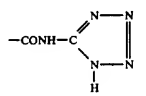
with a compound containing an available pharmaceutically acceptable cation and capable of converting the group X to a pharmaceutically acceptable salt of an E group.

Compounds capable of converting the group X to a pharmaceutically acceptable salt of an E group include compounds, e.g. bases and ion exchange resins, containing pharmaceutically acceptable cations, e.g. sodium, potassium, calcium, ammonium and appropriate nitrogen containing organic cations. In general we prefer to form the pharmaceutically acceptable salt by treating the free acid of formula I with an appropriate base, e.g with an alkaline-earth or alkali metal hydroxide, carbonate or bicarbonate in aqueous solution or by a metathetical process with an appropriate salt. When a strongly basic compound is used care should be taken, e.g by keeping the temperature sufficiently low, to ensure that the compound of formula I is not hydrolysed or otherwise degraded. The pharmaceutically acceptable salt may be recovered from the reaction mixture by, for example, solvent precipitation and/or removal of the solvent by evaporation, e.g by freeze drying.

According to our invention we also provide a pharmaceutical composition comprising (preferably less than 80%, and more preferably less than 50% by weight) of a compound of formula I, or a pharmaceutically acceptable derivative thereof, in combination with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of suitable adjuvants, diluents or carriers are:- for tablets capsules and dragées; microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin; for suppositories, natural or hardened oils or waxes; and for inhalation compositions, coarse lactose. The compound of formula I, or the pharmaceutically acceptable derivative thereof, preferably is in a form having a mass median diameter of from 0.01 to 10 microns. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilizers, sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form. We prefer compositions which are designed to be taken oesophagally and to release their contents in the gastrointestinal tract.

The 5-tetrazolyl and (N-tetrazol-5-yl)carboxamido groups are of formulae XVII and XVIII respectively,

XVII



XVIII

The groups of formulae XVII and XVIII may exist in tautomeric forms and such tautomeric forms are included within the definition of the compounds of formula I.

The invention is illustrated, but in no way limited by the following Examples.

EXAMPLE 1

4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(a) 4-Acetamido-2-allyloxyacetophenone

4-Acetamido-2-hydroxyacetophenone (19.3 g) allyl bromide (12.1 ml) and anhydrous potassium carbonate (21.5 g) were stirred in dry dimethylformamide (250 ml) at room temperature for 24 hours. The reaction mixture was poured into water and the product was extracted with ethyl acetate. The organic solution was then washed well with water dried over magnesium sulphate and evaporated to dryness. The sub-title product was obtained as buff coloured solid (20.5 g). The structure of

the product was confirmed by NMR and mass spectroscopy.

(b) 4-Acetamido-3-allyl-2-hydroxyacetophenone

The above allyl ether (18.4 g) was heated at 200°-210° C. for 4 hours. 17.1 g of the thermally rearranged sub-title product was obtained as a brown solid. Again the structure was confirmed by NMR and mass spectroscopy.

(c) 4-Acetamido-2-hydroxy-3-propyl acetophenone

The product of step (b) (17 g) was dissolved in glacial acetic acid and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through a kieselguhr filter and the filtrate was evaporated to leave 13.0 g of almost colourless solid. The mass and NMR spectra confirmed the structure of the product.

(d) Ethyl 7-acetamido-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A mixture of diethyl oxalate (19.3 g; 17.9 ml) and the above product of step (c) (12.4 g) in dry ethanol (100 ml) was added to a stirred solution of sodium ethoxide in ethanol (prepared by dissolving sodium (6.1 g) in dry ethanol (200 ml)). The reaction mixture was refluxed for 3 hours and then poured into dilute hydrochloric acid and chloroform. The chloroform layer was separated, washed with water and dried. The solvent was evaporated to leave a brown solid which was dissolved in ethanol (300 ml) containing concentrated hydrochloric acid (3 ml) and the whole was refluxed for 1 hour. The reaction mixture was poured into water and the product was extracted into ethyl acetate which was washed with water and dried. The solvent was evaporated to leave 10 g of a sticky solid which had mass and NMR spectra consistent with the expected product.

(e) Ethyl 7-amino-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A solution of the amide of step (d) (10 g) in ethanol (300 ml), containing concentrated hydrochloric acid (5 ml), was refluxed for 8 hours. The reaction mixture was diluted with water and extracted into ethyl acetate. The extract was washed with water, dried and the solvent was evaporated to leave a dark brown semisolid. This was chromatographed on a silica gel column, using ether as eluant to give 4.8 g of the required product whose structure was confirmed by mass and NMR spectral evidence; mp 84°-87° C.

(f) 8-Ethoxycarbonyl-2-methoxycarbonyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline

The amino benzopyran of step (e) (2.0 g) and dimethyl acetylene dicarboxylate (1.24 g; 1.01 ml) were refluxed in ethanol (30 ml) for 26 hours. The reaction mixture was cooled to 0° C. and the insoluble yellow-brown solid was collected by filtration and washed with a little ethanol and dried to give 2.0 g of a product which was a mixture of maleic and fumaric esters obtained by Michael addition of the amine to the acetylene.

This mixture of esters (2.0 g) was treated with polyphosphoric acid (30 ml) and heated on the steam bath with stirring for 20 minutes. The reaction mixture was then poured onto ice and stirred with ethyl acetate. The organic layer was separated, washed with water and dried. The solvent was evaporated to leave 1.6 g of a yellow orange solid. Recrystallisation of this solid from ethyl acetate gave the required product as fluffy orange needles mp 187°-188° C.

Analysis Found: C, 62.0%; H, 5.1%; H, 3.7%: $C_{20}H_{19}NO_7$ Required: C 62.3%; H, 4.9%; N, 3.6%.

(g) 4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (2.5 g) was refluxed with sodium bicarbonate (1.64 g) in ethanol (100 ml) and water (50 ml) for 1½ hours. The whole was poured into water and acidified to precipitate a gelatinous solid. This was collected by filtration, refluxed with ethanol and the product was separated by centrifugation (1.4 g) mp 303°-304° C. dec. The structure of the product was confirmed by mass and NMR evidence.

(h) Disodium 4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The bis acid from step (g) (1.35 g) and sodium bicarbonate (0.661 g) in water (150 ml) were warmed and stirred until a clear solution was obtained. This solution was filtered and the filtrate was freeze dried to give 1.43 g of the required disodium salt.

Analysis Found: C, 46.1%; H, 4.0%; N, 2.9%: $C_{17}H_{11}NO_7Na_2$ 12.5% H_2O required: C, 46.1%; H, 3.8%; N, 3.15%.

EXAMPLE 2

4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(a) 4-(N-Acetyl-N-ethyl)amino-2-allyloxyacetophenone

4-(N-acetyl-N-ethyl)amino-2-hydroxyacetophenone (92.6 g), allyl bromide (51 mls) and anhydrous potassium carbonate (90.4 g) were stirred in dry dimethylformamide (500 mls) for 17 hours. The reaction mixture was poured into water and the product was extracted with ether. The organic solution was then washed well with water, dried over magnesium sulphate and evaporated to dryness. The product was obtained as an oil (102.5 g). The structure of the product was confirmed by NMR and mass spectroscopy.

(b) 4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone

The allyl ether product of step (a) (100.5 g) was refluxed in diethylaniline (300 mls) for 3 hours. The reaction mixture was cooled and poured into dilute hydrochloric acid and extracted into ether, which latter was washed with dilute hydrochloric acid, and then with water. The organic solution was extracted with 10% sodium hydroxide solution which was then acidified. The precipitated product was extracted with ether which was dried over magnesium sulphate. The resulting ethereal solution was evaporated to dryness to give a yellow-brown oil (78.7 g). This oil was a mixture of 4-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone and 6-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone.

This mixture was dissolved in ethanol (500 mls) and glacial acetic acid (20 mls) and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through kieselguhr and the filtrate evaporated to leave 79.9 g of brown oil. This brown oil was a mixture and was separated by high pressure liquid chromatography using ether/petroleum ether (1:1) as solvent to give 44.2 g of the sub-title compound and 23.8 g of 6-(N-acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone.

(c) 4-N-Ethylamino-3-propyl-2-hydroxyacetophenone

4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone (44 g) was refluxed in 48% hydrogen bromide in glacial acetic acid (100 mls), glacial acetic acid (500 mls) and water (20 mls) for 6 hours. The reaction mixture was poured on to ice-water and extracted with ethyl acetate which was washed with water, sodium bicarbonate solution, then water again and dried over magnesium sulphate. The organic solvent was evaporated to dryness to leave the sub-title compound as a red oil (34 g). The structure was confirmed by NMR and mass spectroscopy.

(d) Methyl 6-acetyl-1-ethyl-7-hydroxy-4-oxo-8-propyl-4H-quinoline-2-carboxylate

The amine product of step (c) (17 g) and dimethacetylenedicarboxylate (11.3 mls) were refluxed in ethanol (300 mls) for 17 hrs. The reaction mixture was cooled and evaporated to dryness to leave a deep red oil. This oil was chromatographed on a silica gel column using ether/petroleum ether (1:1) as eluant to give 19.1 g of dimethyl 1-(4-acetyl-3-hydroxy-2-propylphenyl)-N-ethylaminomaleate m.p. 83°–87° C.

The maleic ester (5 g) was heated and stirred in polyphosphoric acid (100 mls) on the steam bath for 10 minutes. The reaction mixture was cooled and poured on to a mixture of ice-water and ethyl acetate. The organic solution was separated, washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave a pale yellow solid. This product was purified by high pressure liquid chromatography to give 2.6 g of the sub title compound m.p. 121°–123° C.

Analysis Found: C: 65.5%; H; 6.6%; N; 4.2%: $C_{18}H_2NO_5$ Required: C: 65.3%; H; 6.34%; N; 4.23%.

Methyl 6-acetyl-1-ethyl-5-hydroxy-4-oxo-4H-quinoline-2-carboxylate was obtained from the purification as a pale yellow solid (100 mgs).

(e) Diethyl 4,6-dioxo-1-ethyl-10-propyl-4H-6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The hydroxy ketone product of step (d) (1.0 g) and diethyl oxalate (3.3 mls) in dry dimethylformamide (25 mls) were added to ether washed 50% sodium hydride (0.581 g) in dry dimethylformamide (20 mls) and the reaction mixture stirred for 4 hours. The reaction mixture was then poured into water, acidified and extracted with ethyl acetate, which was then washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to give an oil which was dissolved in ethanol (100 mls) and concentrated hydrochloric acid (a few drops) added. The solution was refluxed for ½ hr, cooled, poured into water and extracted with ethyl acetate, which was washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave an oil which solidified on trituration with 40°–60° petroleum ether (1.2 g). The structure of the compound was confirmed by NMR.

(f) 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (1.0 g) and sodium bicarbonate (0.787 g) in ethanol (85 mls) and water (32 mls) were refluxed for 4 hours. The reaction mixture was poured into water, acidified and the precipitate was collected by filtration and dried. The product was purified by triturating with boiling ethanol, then twice with boiling acetone. After each trituration the mixture was centrifuged and the supernatant liquid was removed by decantation. The residual solid was dried to give 0.547 g of the required di-acid as a yellow powder m.p. 298°–300° C. dec.

Analysis: Found: C: 61.3% H; 5.0% N; 3.6%: $C_{19}H_{17}NO_7$ Required: C: 61.5% H; 4.6% N; 3.79%.

(g) Disodium 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The above di-acid (4.098 g), suspended in water (100 mls) and was treated with sodium bicarbonate (1.82 g). The resulting solution was filtered and the filtrate was treated with acetone until complete precipitation of the product had occurred. The required di-sodium salt was filtered off and dried to give 3.39 g of a pale yellow powder.

Analysis: Found: C: 51.1%; H; 4.3%; N; 3.0%: $C_{19}H_{15}MN_2O_7$ Required: C: 51.1%; H; 4.1%; N; 3.1% (6.9% water).

EXAMPLE 3

The following compounds may also be made by the processes described above:

(i) 5-Ethyl-4,8-dioxo-10-propyl-4H,8H-pyrano[2,3-h]quinoline-2,6-dicarboxylic acid

(ii) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-dicarboxylic acid

(iii) 10-Bromo-4,6-dioxo-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(iv) 5-Hydroxy-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid ;P1

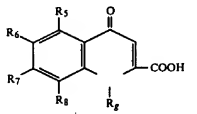
(v) 4,9-Dioxo-4H,9H-pyrano[2,3-g]quinoline-2,7-dicarboxylic acid

(vi) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-di[N-(tetrazol-5-yl)]carboxamide

(vii) 10-Bromo-4,6-dioxo-2,8-di-(tetrazol-5-yl)-4H,6H-pyrano[3,2-g]quinoline.

We claim:

1. A compound having the formula



in which R_6 and R_7 form a chain —COCH=C-(COOH)—O—,

R_5 and R_8, which may be the same or different, are sterically compatible substituents selected from hydrogen and alkyl having up to 8 carbon atoms, and

R_g is hydrogen or alkyl having up to 8 carbon atoms, and pharmaceutically acceptable salts and ethyl esters thereof.

2. A compound according to claim 1, wherein each of R_5, R_8 and R_g, when they are alkyl, contain up to 4 carbon atoms.

3. A compound according to claim 1, wherein the —COCH=C(COOH)—O— chain is bonded with the —O— end thereof in position R_7.

4. A compound according to claim 1, wherein R_5 and R_8 are selected from hydrogen and propyl.

5. A compound according to claim 1, wherein R_g is ethyl.

6. 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof.

7. 4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition suitable for the treatment of a condition involving an antibody antigen reaction or a reflex pathway comprising an effective amount of a compound according to claim 1 in combination with a pharmmaceutically acceptable adjuvant, diluent or carrier.

9. A composition according to claim 8 comprising less than 80% by weight of active ingredient.

10. A composition comprising from 0.01 mg to 50 mg of a compound according to claim 1, as active ingredient, in unit dosage form.

11. A method of treatment of a condition involving an antibody antigen reaction or a reflex pathway, which comprises administering an effective amount of a compound according to claim 1 to an animal suffering from such a condition.

* * * * *

APPENDIX 4

Certificate of Correction on
U.S. Patent No. 4,474,787 and
Pending Request for a Certificate
of Correction filed February 17, 1993

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,474,787
DATED : October 2, 1984
INVENTOR(S) : HUGH CAIRNS ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5, line 36, "an an" should be --and an--.

Column 9, line 33, "-CH" should be -- -OH --.

Column 16, line 15, " $C_{19}H_{15}MN_2O_7$", should be

--$C_{19}H_{15}NNa_2O_2$--.

Signed and Sealed this

Ninth Day of April 1985

[SEAL]

Attest:

Attesting Officer

DONALD J. QUIGG

Acting Commissioner of Patents and Trademarks

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 4,474,787 Granted October 2, 1984	)	7,6 DIOXO-4H,6H,PYRANO [3,2-g]QUINOLINE DICARBOXYLIC ACIDS AND ANTI-ALLERGIC USE THEREOF
U.S. Serial No. 06/344,982 Filed February 2, 1982	)	Group Art Unit 129 Examiner: Daniel B. Springer

REQUEST FOR CERTIFICATE OF CORRECTION UNDER RULE 322

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

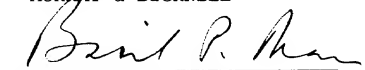
Sir:

Patentees respectfully request a Certificate of Correction to be issued for the above-identified U.S. Patent correcting the patent as noted in the attached "Certificate of Correction" Form PTO 1050 (Rev. 3-82). Duplicate copies of the form are attached hereto.

The error is the fault of the Patent Office. The correct structural formula of the compound was given in claim 17 (Amendment A, March 11, 1983), which appears as claim 1 of the issued patent.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BICKNELL

By 

Basil P. Mann (18,464)
A Member of the Firm
Attorneys for Applicant(s)
Two First National Plaza
Chicago, Illinois 60603
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Chicago, Illinois
Feb. 17, 1993
42489

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CERTIFICATE OF CORRECTION

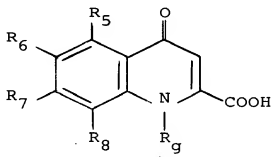
PATENT NO. : 4,474,787

DATED : October 2, 1984

INVENTOR(S) : HUGH CAIRNS ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, claim 1, the structural formula should be as follows:



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Marshall, O'Toole et al.
Two First National Plaza, Suite 2100
Chicago, Illinois 60603

PATENT NO. 4,474,787

No. of add'l. copies @ 30¢ per page

FORM PTO 1050 (REV. 3-82)

APPENDIX 5

Maintenance payment receipts on
U.S. Patent No. 4,474,787

UNITED STATES DEPARTMENT OF COMMERCE
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ITM NBR	PATENT NUMBER	FEE COD	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,474,787	170	225	----	06/346,982	10/02/84	02/02/82	04	NO	PAID
2	4,474,502	173	450	----	06/435,224	10/02/84	10/19/82	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	6181
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1	4,474,787	170	225	----	06/348,982	10/02/84	02/02/82	04	NO	PAID
2	4,474,502	173	450	----	06/498,116	10/02/84	05/10/83	04	NO	PAID

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,424,787	170	225	----	06/348,982	10/02/84	02/02/82	04	NO	PAID
2	4,474,502	170	450	----	06/433,226	10/02/84	01/13/82	04	NO	PAID

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,474,387	170	225	----	06/343,932	10/02/84	02/02/82	04	NO	PAID
2	4,474,502	173	450	----	06/453,224	10/02/84	01/14/83	04	NO	PAID

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03/29/88

041104

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenence fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the releted patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,474,787	170	225	----	06/346,982	10/02/84	02/02/82	04	NO	PAID
2	4,474,802	173	450	----	06/458,126	10/02/84	01/17/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an esterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	6181
2	

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000197

COMPUTER PATENT ANNUITIES
% COMPUTER PATENT ANNUITIES LIMITED
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514
ARLINGTON, VA 22202

DATE MAILED
08/29/88

041104

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,474,787	170	225	----	06/240,442	10/02/84	02/02/82	04	NO	PAID
2	4,474,803	173	450	----	06/455,226	10/02/84	01/03/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	5181
2	

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000197

COMPUTER PATENT ANNUITIES
% COMPUTER PATENT ANNUITIES INCORP.
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514
ARLINGTON, VA 22202

DATE MAILED
03/29/88

941104

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,474,787	170	225	----	06/344,982	10/02/84	02/02/82	04	NO	PAID
2	4,474,802	173	450	----	06/453,126	10/02/84	01/13/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	6181
2	

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APPENDIX 6

Clinical trials undertaken under
IND 21,544 together and
submissions to the FDA under NDA 19-660
between 30 October 1986 and 30 November 1992

U.S. Clinical Trials for Tilade® Inhaler

The U.S. clinical program was initiated on April 11, 1983 with submission of the first clinical protocol under IND 21,544 for Study CR 587. Below is a list of all clinical studies conducted under the IND:

Study No.	Start Date	Finish Date
CR 587	01-JUN-83	01-OCT-83
CR 718	01-FEB-84	01-APR-84
CR 813	01-MAY-84	01-DEC-84
CR 891	15-DEC-84	15-MAY-85
CR 940	15-JUN-85	15-JUN-86
CR 969	01-JUL-85	01-OCT-85
CR 970*	01-DEC-85	01-JUN-87
CR 971	15-MAR-85	15-JUN-85
CR 1070**	01-SEP-86	30-MAY-88
CR 1072	15-FEB-86	15-JUL-87
CR 1086	15-SEP-87	15-AUG-88
CR 1087	10-JAN-86	21-JAN-86
CR 1281*	01-SEP-87	01-DEC-90
CR 1356	17-OCT-87	01-FEB-89
CR 1357*	17-OCT-87	31-MAR-89
CR 1386	15-NOV-87	31-JAN-89
CR 1416**	01-JAN-88	20-FEB-89
CR 1599	25-APR-90	ONGOING
CR 1648*	17-JUN-89	30-AUG-90
CR 1667*	31-DEC-89	18-JAN-91
CR 1873*	01-MAY-89	01-SEP-90
CR 1948*	30-MAY-89	31-JUL-90
CR 1998*	15-JAN-90	30-JUN-90 (DISCONTINUED)
CR 2004*	01-JAN-91	01-AUG-91
CR 2075*	20-DEC-90	30-JUN-91
CR 2081*	01-DEC-89	01-SEP-90
CR 2181	30-JUL-91	ONGOING
CR 2212	30-SEP-91	ONGOING
CR 2255	30-OCT-91	ONGOING
CR 2264	26-NOV-91	ONGOING
CR 2279	15-DEC-91	ONGOING
CR 2336/2337	17-AUG-92	ONGOING
CR 2338	21-SEP-92	ONGOING
CR 2340*	22-JUN-92	30-OCT-92
TS 100*	12-FEB-90	01-MAR-91
TS 102*	13-JUL-90	01-MAR-91

*Final medical report pending, data from study **not** included in NDA safety database
**Final medical report pending, data from study included in NDA safety database

Submissions Under NDA 19-660
Tilade® Inhaler

Date	Description
October 30, 1986	Submission of the (pre-NDA) chemistry, manufacturing and controls section 90-120 days before anticipated submission of the remainder of the new drug application.
February 27, 1987	Original NDA Submission.
April 30, 1987	Additional preclinical data (SE 6535/1).
May 1, 1987	All CRFs for US Study No. 701B, C & D (Requested by Dr. Hoberman).
May 11, 1987	All CRFs for US Study No. 84-754 (Group III) (Requested by Dr. Hoberman.
May 12, 1987	Requested by Dr. Straus: 1) Additional data for US Study No. 84-754 (Group III) concerning the percentage predicted FEV_1 values. 2) Additional data for US Study No. 701 concerning abnormal laboratory values.
June 11, 1987	Response to Dr. Clyde Oberlander's (FDA) telephone comments on May 13, 1987 concerning the expression of lethal dose in Safety Evaluation (SE) 5338.
July 8, 1987	Requested by Dr. Hoberman: 1) Additional statistical analyses for US Study No. 84 754 (Groups I-III) on the patients bi-weekly mean diary symptom scores for daytime asthma, nighttime asthma and cough over the final eight weeks of treatment. 2) Reference for the Mack-Skillings tests which were used in the analysis of the foreign trials.
July 17, 1987	Requested by Dr. Straus: Tables demonstrating the maximum percentage decrease in FEV_1, after challenge for each patient in SD 4943/A (Cold Air Challenge Study).

Date	Description
August 18, 1987	Requested by Dr. Hoberman: Information includes for each domestic therapeutic study (#701 and #84-754), a tabulation of the number of patients who improved or deteriorated from baseline based on the patient's diary scores for the baseline period, and the final two weeks of double-blind treatment.
August 21, 1987	Requested by Dr. Antoine El Hage, Division of Scientific Investigations: Forms FDA 1573, curricula vitae and protocols for Studies SDs 10508, 10509 and 10510 (US #84-754) as submitted in the original NDA.
August 26, 1987	Requested by Dr. Antoine El Hage, Division of scientific Investigations: Raw data for the first five patients receiving active drug in SDs 10508, 10509 and 10510 (US #84-754)
August 27, 1987	Notification to the Division of Surgical-Dental Drug Products of the information sent to Dr. Antoine El Hage (Division of Scientific Investigations) on August 21 and 26, 1987.
September 18, 1987	Response to FDA letter of September 14, 1987 concerning revisions to the draft package circular under the PRECAUTIONS and OVERDOSAGE sections and comments concerning a literature article (revised draft package circular submitted).
September 24, 1987	Response to FDA letter of August 17, 1987 with chemistry, manufacturing and control comments (microbiological concerns).
October 14, 1987	120 Day Safety Update Report and medical synopsis of each of six recent Tilade therapeutic trials (SDs 10662, 10664, 10665, 10638, 10636, 10549). Also included was a listing of foreign post-marketing adverse experience reports received for Tilade by Fisons plc (cross-referred to IND 21,544 for submission of full reports of these therapeutic trials. These were submitted on November 4, 1987 under IND 21,544).
October 15, 1987	Response to telephone comments received on October 14, 1987 from Vivian Greenman (FDA) concerning our September 24, 1987 response to microbiological concerns.

Date	Description
October 29, 1987	Requested by Dr. Straus: Re-analysis of data for US Study Nos. 701 and 84-754 regarding combining a group of three symptom scores as one and also for information concerning the use of corticosteroids in SD No. 4795/A (CR No. 767).
November 17, 1987	Revised Fisons Corporation finished product specifications. The revisions concern the Microbiological Test.
January 15, 1988	Response to FDA letter of October 13, 1987 (chemistry, manufacturing and control comments). Response included stability data, revised finished product specifications and a revised package circular.
February 2, 1988	Letter of cross-reference to DMF 1812 for Fisons Corporation, Bedford Massachusetts.
July 15, 1988	Letter informing Division of an upcoming submission of a Clinical Amendment.
August 23, 1988	Clinical Amendment: Submission of results of four clinical trials: SD 10950 (Tilade Inhaler vs. Intal® Inhaler vs. placebo) SD 10974; SD 10662; SD 10765
August 29, 1988	Desk copy of August 23, 1988 submission sent to Conrad Ledet, Consumer Safety Officer (FDA)
September 19, 1988	Response to Dr. Hoberman's September 12, and 13, 1988 telephone calls which included contingency tables showing the number of patients in each treatment group for SD 10950 who worsened by 1.00 or more points and those who did not for specified diary variables.
September 21, 1988	Response to Dr. Straus' September 20, 1988 telephone call which included confidence intervals for the Intal Inhaler vs. Placebo comparison for SD 10950.
October 12, 1988	Additional patent information (Patent No. 4,760,072).
November 10, 1988	Response to FDA letter of June 14, 1988 (chemistry, manufacturing and control comments). Response included updated specifications and methods for drug substance and finished product, stability data, container-closure system information and a revised package circular.

Date	Description
November 30, 1988	Amendment to November 10, 1988 submission which included revised Fisons Corporation specifications.
December 2, 1988	Requested by Dr. Straus: A presentation of confidence intervals for the difference in the proportion improving by 1.0 points or more, a presentation of the chemical structures of nedocromil sodium and cromolyn sodium and also schematics of six therapeutic trials.
March 29, 1989	Notification of change of address for correspondence to Rochester, New York.
April 7, 1989	Response to FDA letter of February 6, 1989 (chemistry, manufacturing and control comments). Response included information on container closure system, revised finished product specifications and methods, stability data and methods validation package.
May 16, 1989	Submission to NDA of CFC Petition as submitted on December 23, 1987 to the Dockets Management Branch.
June 12, 1989	Submission to Dockets Management of information on chloroflourocarbons as requested by Adele Seifried (FDA) on May 1, 1989.
December 21, 1989	Response to FDA letter of September 12, 1989 (chemistry, manufacturing and control comments). Response included container-closure information, revised finished product specifications, stability testing information and information on particle size distribution test.
March 1, 1990	Letter to Division regarding February 23, 1990 meeting between the Division and Fisons concerning chemistry, manufacturing and control issues.
March 13, 1990	Draft minutes of February 23, 1990 meeting submitted to the Division for review.
April 5, 1990	A copy of the Environmental Impact Analysis Report (EIAR) which was included in original application was submitted to Dockets Management Branch.
April 18, 1990	Letter of authorization to refer to DMF 1557 for Fisons plc, United Kingdom.

Date	Description
April 20, 1990	Minutes of February 23, 1990 meeting between the Division and Fisons concerning chemistry, manufacturing and control issues.
May 7, 1990	Requested by Dr. Hoberman: Plots of the empirical cumulative distribution functions for the change from baseline scores on a bi-weekly basis for daytime asthma, nighttime asthma, cough and concomitant medication use for US Study No. 85-36 (SD 10950).
May 9, 1990	Requested by Dr. Straus: Literature article entitled "Inhibition of sulphur dioxide-induced bronchoconstriction by nedocromil sodium and sodium cromoglycate in non-asthmatic, atopic subjects".
May 14, 1990	Submission of a list of 14 clinical questions conveyed by Mr. Conrad Ledet, CSO, to Dr. Robert Parker, Senior Director Regulatory Affairs, Fisons Corporation, by telephone on May 11, 1990.
May 14, 1990	Submission of draft version of the summary document for the Pulmonary-Allergy Drugs Advisory Committee for the June 11, 1990 Advisory Committee meeting.
May 15, 1990	Requested by Dr. Straus: Copies of CRFs for patients that were treatment failures for Fisons Study No. 85-36 (SD 10950).
June 5, 1990	Fisons' agenda for our presentation at the Pulmonary-Allergy Drugs Advisory Committee Meeting on June 11, 1990.
July 31, 1990	Patent information (Patent No. 4,918,078).
August 3, 1990	Response to Division's May 11, 1990 and July 2, 1990 telephone requests (medical/clinical comments). Response included answers to clinical and statistical questions, certain case report forms as requested and draft Summary Basis of Approval (SBA). (Certain information provided on diskette).
August 30, 1990	Resubmission of a copy of the diskette from August 3, 1990 submission as requested by Dr. Straus during a telephone conversation on August 29, 1990.

Date	Description
August 31, 1990	Response to FDA letter of April 5, 1990 (chemistry, manufacturing and control comments). Response included information concerning particle size analysis, PNAs, revised finished product specifications and methods and stability data.
September 10, 1990	Requested by Dr. Straus: Ten diskettes containing SAS data sets for two studies: US No. 84-754 (SD 10509) US No. 85-36 (SD 10950)
September 24, 1990	Request for a meeting concerning status of NDA.
October 9, 1990	Requested by Dr. Straus: Reanalysis of US Study No. 84-754 (SD 10509) excluding patients who did not meet the reversibility entry criterion for the study (Hard copy and diskette).
October 15, 1990	Submission of NDA Safety Update Report and reports of 36 clinical studies that had recently been compiled. A list was also included of all ongoing trials which included studies still being conducted as well as those pending final reports.
November 8, 1990	Requested by Dr. Hoberman: Reanalysis of Study SD No. 10509, No. 701, and SD No. 10950 (Hard copy and diskette).
November 8, 1990	Requested by Dr. Straus: Data on diskette from the October 15, 1990 Safety Update submission (Volume 22). An additional copy of Volume 17 from October 15, 1990 submission with the draft Summary Basis of Approval (SBA) and copies of foreign labeling, and an additional copy of the diskette with the draft SBA was also submitted.
November 8, 1990	Letter requesting discussion of Tilade NDA and Division review priorities with Dr. Gregory Burke (FDA).
November 13, 1990	Requested by Dr. Straus/Dr. Hoberman: Reanalysis of Fisons Studies SD 10950 and SD 10509 based on the exclusion of six additional patients (Hard copy and diskette).
November 16, 1990	Amendment to Environment Assessment as requested by Dr. Phillip Vincent, Environmental Assessment Officer (FDA).

Date	Description
November 26, 1990	Patent Information (Patent No. 4,918,078).
December 6, 1990	Requested by Dr. Hoberman: Additional desk copy and diskette of our November 13, 1990 submission.
December 10, 1990	Response to FDA letter of November 23, 1990 concerning low first actuations of inhalation aerosols.
December 20, 1990	Copy of December 10, 1990 submission sent to Dr. Guiragos Poochikian, Reviewing Chemist (FDA).
December 20, 1990	Letter to the Division (Dr. G. Burke) requesting the status of outstanding issues concerning the Tilade NDA.
January 25, 1991	Requested by the Division: Resubmission of information provided in our August 3, 1990 submission concerning distribution for missing data for patients who were included in the analysis for Studies 701B (SD 4812/1), 84-754 (SD 10509), and 85-36 (SD 10950).
February 1, 1991	Letter to Dr. M.A. Goheer, Pharmacologist (FDA) in follow-up to a January 31, 1991 telephone communication concerning our carcinogenicity studies.
February 1, 1991	Requested by the Division: 1) Revised draft labeling that reflects discussion at the June 1990 Advisory Committee Meeting. Copies of all labeling used in foreign countries where Tilade Inhaler is approved were also included. 2) Copies of last submitted Annual Reports for all nedocromil products under an open IND.
February 1, 1991	Letter to Division (Dr. G. Burke) requesting the status of certain Tilade issues.
February 5, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO which contained a copy of the February 1, 1991 letter to Dr. G. Burke (FDA).
February 6, 1991	Requested by the Division: Submission on diskette of the draft text of the package circular, references and patient instructions as submitted to the Division on February 1, 1991.

Date	Description
February 7, 1991	Desk copy of Section 2.E. and Section 4 (Nonclinical Pharmacology and Toxicology) from original NDA submission of February 27, 1987 sent to Mr. Joseph Buccine, CSO (FDA) as requested.
February 14, 1991	Requested by the Division: 1) Case report forms representing all patient deaths that occurred in reported NDA clinical studies and representing all patients in clinical studies who received Tilade and were withdrawn for reasons of fatigue, depression, abdominal pain, dyspepsia and tremor. 2) Additional information in reference to the October 15, 1990 Safety Update: • Unusual events categorized by study for controlled clinical trials involving Tilade and placebo as specified. • Additional formats of SAS data sets for adverse experience data submitted with the October 1990 Safety Update Report (Hard copy and diskette).
February 22, 1991	Requested by the Division: 1) SAS data sets for three-month animal safety studies (hard copy and diskette). 2) A listing of user terms designated under the WHO classification for chest pain. 3) Discussion of a request by Dr. Sherwin Straus (FDA) for the data base for the clinical study described in a literature article.
March 5, 1991	Letter to the Division (Dr. G. Burke) requesting clarification of the approvability of the application.
March 6, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) which contained a copy of the March 5, 1991 letter to Dr. Burke.
March 8, 1991	Response to comments received from the Division on February 25, 1991 by facsimile transmission concerning the adequacy of the mouse 21-month carcinogenicity study submitted in the Tilade Inhaler NDA.
March 8, 1991	Requested by Dr. Straus: Tabulations for the liver function test data from US studies (hard copy and diskette.

Date	Description
March 12, 1991	Letter to the Division requesting a meeting with the reviewing Chemist to discuss the contents of the February 27, 1991 letter from the Division which commented on manufacturing and control deficiencies.
March 15, 1991	Requested by Dr. Straus: 1) Listing of all patients reporting adverse events coded as arthralgia, arthritis or arthritis rheumatoid in controlled studies for Tilade and a listing of other events reported by these patients. 2) Listing of patients withdrawing from Tilade clinical trials, reported separately for patients less than and greater than fifty years old due to headache, diarrhea, vomiting, taste perversion, nausea, pharyngitis or fatigue. 3) Listing of patients withdrawn due to unusual events from placebo controlled studies with Tilade taken at doses of 4mg QID. 4) Background information on the Tilarin® (nedocromil sodium nasal spray; IND 26,651) SGPT data set.
March 25, 1991	Letter to the Division confirming initial labeling discussions with the Division scheduled for March 28, 1991. (List of attendees included).
April 2, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) consisting of portions from our February 14, 1991 submission.
April 4, 1991	Requested by the Carcinogenicity Assessment Committee (FDA): Copies of three preclinical studies on cromolyn as originally submitted under NDA 16-990 Intal® Capsules and referred to in subsequent applications for cromolyn sodium drug products.
April 15, 1991	1) Revised draft labeling (hard copy and diskette) reflecting the labeling changes agreed to be made at the March 28, 1991 meeting with the Division. 2) Summaries of clinical safety data: • Tilade use in pregnancy. • Isolated cases of transaminase elevation with Tilade Inhaler - A Review. 3) English translations of previously submitted foreign labeling.

Date	Description
April 26, 1991	Six desk copies of April 15, 1991 submission sent to Mr. Joseph Buccine, CSO (FDA) as requested.
May 6, 1991	Response to FDA letter of February 27, 1991 (chemistry, manufacturing and control comments). Response included adding Rochester, NY as an alternative to Bedford, MA for US testing of Tilade, revised specifications and methods and information/data concerning particle dispersion.
May 8, 1991	Letter to the Division (Dr. G. Burke) requesting clarification of the approvability of the application.
May 17, 1991	Requested by the Division: 1) A list of all patients with creatinine greater than 2.5. 2) A list of all patients with an increase in eosinophils from baseline of more than 10%. 3) A list of patients with WBC less than 500 at any time. 4) A list of patients with platelets less than 75,000 anytime. 5) A list of studies with EKG data. 6) All hematology data. 7) Inclusion of dose as a variable in a previously submitted data set (hard copy and diskette). 8) Attachments not included in April 15, 1991 submission.
May 31, 1991	Requested by the Division: 1) Specific adverse event preferred terms for patients not withdrawn from clinical trials due to adverse events (diskette). 2) Table 4 from the October 15, 1990 Safety Update excluding dropouts and including doses in total mg (diskette). 3) CRFs for patients of the total safety data base who experienced certain specified adverse events and CRFs for Tilade patients withdrawn for reasons as specified.
June 4, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) with a chronological listing of clinical submissions under the NDA for Tilade Inhaler.
June 7 and 10, 1991	Facsimile transmissions to Mr. Joseph Buccine, CSO (FDA) with copy of Dr. Zimmerman's (Fisons Corporation's consultant) report regarding hepatotoxicity.

Date	Description
June 13, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA), summarizing recent meetings and telephone communications with the Division.
June 13, 1991	Submission of report by Dr. Hyman Zimmerman (Fisons Corporation's consultant) regarding the effects of Tilade on the liver.
June 14, 1991	A listing of clinical trials which were identified in the Tilade Unusual Events Summary which was part of the October 15, 1990 Safety Update Report. The listing notes which of these were submitted under NDA 19-660 and when.
June 18, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) which included a page from a case report form for Patient 1073, CR 1092 from our February 14, 1991 submission which was inadvertently not included.
June 19, 1991	Case report form for a patient which was not included with our May 31, 1991 submission (Patient LY05 from CR 940).
June 21, 1991	Requested by Dr. G. Turner Division of Scientific Investigations: Case report forms for all subjects entered into CR1072 (SD 10950) from sites as specified with a copy of the protocol and amendments for this study.
June 21, 1991	Notification to the Division of Oncology and Pulmonary Drug Products of the documentation sent to Dr. G. Turner (Division of Scientific Investigations) on June 21, 1991.
July 3, 1991	Revised draft labeling as requested by the Division.
July 10, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of the data sheet for Tilade from the ASPI Data Sheet (1990-91 issue) as requested.
July 11, 1991	Position paper which discusses the rationale behind, and the justification for, the dose selection in the 21-month mouse carcinogenicity study.
July 11, 1991	Facsimile transmission of revised draft labeling in response to the draft labeling received from the Division by facsimile on July 3, 1991. Confirmation of attendees for the July 12, 1991 meeting between Fisons and the Division is also included.

Date	Description
July 11, 1991	Documentation submitted to Dr. Alan Taylor, Supervisory Pharmacologist (FDA) which supports the presence of an effect of nedocromil sodium on various inflammatory cell types and which supports the statements made in the draft labeling.
July 19, 1991	Revised draft labeling in follow-up to July 12, 1991 meeting (hard copy and diskette).
July 23, 1991	Facsimile transmission to Dr. Alan Taylor, Supervisory Pharmacologist (FDA), of copies of journal publications cited as references in our July 19, 1991 draft labeling (as requested).
July 24, 1991	Submission to Mr. Joseph Buccine, CSO (FDA), of an additional diskette of our July 19, 1991 draft labeling (as requested).
August 2, 1991	Facsimile transmission to Dr. G. Poochikian, Deputy Chemistry Supervisor (FDA), which includes draft minutes from the Tilade chemistry meeting on July 31, 1991.
August 2, 1991	Amendment to draft labeling submitted on July 19, 1991 which included revised immediate container labels, cartons and shipper labels.
August 6, 1991	Summary document for the nedocromil sodium rat carcinogenicity study as requested.
August 7, 1991	Letter to Division (Dr. G. Burke) regarding timely resolution of chemistry issues and approvability of the NDA.
August 8, 1991	Submission of minutes of July 31, 1991 meeting with the Division concerning chemistry, manufacturing and control issues. Also included was a response to a number of questions which arose during the meeting.
August 15, 1991	Informal submission to Dr. Sherwin Straus, Medical Officer (FDA), of the draft Medical and Statistical Report for Fisons Study No. 87-11A entitled "A Double-Blind Multicenter Group Comparative Study of the Efficacy and Safety of Tilade® (nedocromil sodium) BID vs. Placebo in the Management of Adults with Reversible Airways Obstruction."

Date	Description
August 20, 1991	Submission of chemistry, manufacturing and control information/data in response to issues discussed at the July 31, 1991 meeting. Included was response to questions from July 31, 1991 meeting and minutes from that meeting, particle size/dispersion data, valve processing information, updated drug substance specifications and methods, updated finished product specifications and methods, updated post-approval stability protocol and a report on the study of effects of valve orientation and time on the first and second sprays of Tilade MDI.
August 21, 1991	Response to telephone comments received on August 16, 1991 by Dr. Alan Taylor, Supervisory Pharmacologist (FDA), regarding the mouse carcinogenicity study.
August 23, 1991	Submission to Dr. Sherwin Straus, Medical Officer (FDA), of a diskette with the SAS data set from Study 87-11A which was sent informally as a draft report to Dr. Straus on August 15, 1991 (as requested by Dr. Straus).
August 28, 1991	Revised draft labeling (hard copy and diskette) which responds to comments in the Division's August 19, 1991 facsimile transmission.
September 5, 1991	Submission to Dr. Sherwin Straus, Medical Officer (FDA), of a diskette with additional SAS data sets from Study 87-11A (as requested by Dr. Straus).
September 5, 1991	Letter to the Division (Dr. G. Burke) regarding the approvability status of the NDA.
September 5, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA), which included a copy of an attachment inadvertently omitted from our August 28, 1991 submission.
September 6, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA), which contained a rationale in support of the method of analysis employed in evaluating the occurrence of withdrawals related to Tilade.
September 12, 1991	Submission of Fisons Corporation's test method FTM 471B (the revised version of the HPLC Stability Indicating Assay of Total Can Content of Nedocromil Sodium and Nedocromil Sodium Related Substances in Tilade Inhaler).

Date	Description
September 13, 1991	Submission of draft labeling in response to a September 10, 1991 facsimile transmission from the Division. Also included for formal submission were documents sent on September 5 and 6, 1991 by facsimile transmission to Mr. Joseph Buccine, CSO (FDA).
September 19, 1991	Letter to the Division informing of submission of the additional Tilade clinical studies to IND 21,544.
September 20, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (with a copy to Dr. Alan Taylor, Supervisory Pharmacologist), of draft revisions to the Carcinogenicity section of the Tilade package circular in response to telephone comments received from Dr. Taylor.
September 23, 1991	Facsimile transmission to Dr. Alan Taylor, Supervisory Pharmacologist (FDA), of draft revisions to the Carcinogenicity section of the Tilade package circular in response to telephone comments received from Dr. Taylor.
September 25, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA), with verification of the patent information filed under the NDA (as requested by Mr. Buccine).
September 26, 1991	Letter to Dr. Robert J. Temple to request a meeting concerning labeling issues.
September 27, 1991	Facsimile transmission to Dr. Alan Taylor, Supervisory Pharmacologist (FDA), of draft revisions to the Carcinogincity section of the Tilade package circular in response to telephone comments received from Dr. Taylor.
September 30, 1991	A listing of adverse events listed in the current version of the Tilade draft package circular broken down by severity (as requested by the Division).
October 7, 1991	Information on patient deaths as requested by Mr. Joseph Buccine, CSO (FDA).
October 9, 1991	Facsimile transmission to Dr. Alan Taylor, Supervisory Pharmacologist (FDA), of further draft revisions to the Carcinogenicity section of the Tilade package circular.
October 10, 1991	A copy of the "Integrated Summary of Effectiveness" from the original Tilade NDA sent to Mr. Joseph Buccine, CSO (FDA), at his request.

Date	Description
October 16, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA), of a listing of all submissions made by Fisons to NDA 19-660 up to October 16, 1991.
October 18, 1991	Submission of a revised version of the HPLC Stability Indicating Assay of Total Can Content of Nedocromil Sodium and Nedocromil Sodium Related Substances in Tilade Inhaler (FTM 471C). Copies of revised Post-Approval Stability Protocol, Analytical Report and Finished Product Specification and Analytical Report were included.
October 22, 1991	Submission of a revised adverse events table from the draft package circular and SAS data sets as requested by Mr. Joseph Buccine, CSO (FDA).
October 23, 1991	Letter to the Division regarding comparative statements made between Tilade and Intal®. Letter requested that SD 11688, the final report of a comparative study of Tilade and Intal be examined and provided a copy of a draft report for study 88-12 involving Tilade and albuterol.
October 24, 1991	Submission of a desk copy of SD11688 previously submitted on September 19, 1991 under IND 21,544 and mentioned in the letter of October 23, 1991 to NDA 19-660.
November 6, 1991	Submission of SAS data sets on diskette from SD 11688 and a corrected version of Table 1 (Trials Included in Unusual Symptom Database) from the October 15, 1990 NDA Safety Update.
November 11, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of the participants and agenda for the meeting with Division Chemists on November 13, 1991.
November 14, 1991	A copy of the October 16, 1991 facsimile transmission of the listing of all submissions to NDA 19-660 and the June 19, 1991 submission of a case report form for Patient L405 from CR 940, as requested by Mr. Joseph Buccine, CSO (FDA) on November 13, 1991.
November 21, 1991	A copy of the corrected Table 1 of studies included in the unusual symptom database submitted November 6, 1991 and a breakdown by dose and duration of Tilade treatment of the studies in Table 1, as requested by Dr. Sherwin Straus, Medical Officer (FDA).
November 25, 1991	Submission of USP biological extractive testing results of the Bespak valve seat and body, as requested by Dr. Alan Taylor, Supervisory Pharmacologist (FDA).

Date	Description
November 25, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of adverse event and withdrawal rates and the number of patients in each category, as requested by Mr. Joseph Buccine.
November 27, 1991	Amendment responding to the Division's letter of October 23, 1991 regarding chemistry, manufacturing and control deficiencies.
December 6, 1991	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of a draft revision to the Carcinogenicity section of the package circular, as requested by Mr. Joseph Buccine on December 4, 1991.
December 13, 1991	Letter to the Division notifying of an update to DMF 6513, Synthesis of Nedocromil Sodium for an alternative route of synthesis and Divisional specifications and analytical methods. Letter commits to only using Route 1 synthesized material for Tilade Inhaler until a supplement is approved to allow use of Route 2.
December 31, 1991	Submission of an updated methods validation package and specifications, procedures and validation documentation for the determination of particle size distribution using an Andersen cascade impactor, and other updated analytical methodology.
January 6, 1991	Submission outlining the most recent submissions of draft labeling. Also included was a list of submissions to NDA 19-660 and IND 21,544 since the October 15, 1990 NDA Safety Update concerning the safety of Tilade Inhaler, and a corrected Adverse Events Table from the package circular submitted on October 22, 1991.
January 6, 1992	Submission to Dr. G. Turner, Division of Scientific Investigations, of the protocol and case report forms for Dr. Lyndon Mansfield for Study Nos. 87-06, 621 and 488.
January 10, 1992	Letter to the Division correcting the particle size distribution specifications submitted December 31, 1991.
January 15, 1992	Letter to the Division concerning the use of inhaled steroids and $beta_2$agonists in asthma therapy and the placement of Tilade in the marketplace.
January 15, 1992	Facsimile transmission to Dr. Young Choi, Reviewing Pharmacologist, (FDA) of a copy of SD 10438 which is a tabular summary of human biopharmaceutics.

Date	Description
January 16, 1992	Facsimile transmission to Dr. Young Choi, Reviewing Pharmacologist, (FDA) of a copy of a section of SD 10442 which contains information from preclinical animal studies on absorption, distribution, metabolism and excretion of nedocromil sodium.
January 16, 1992	Facsimile transmission to Dr. Young Choi, Reviewing Pharmacologist (FDA) of additional information regarding the pharmacokinetics of nedocromil sodium.
January 21, 1992	Letter to the Division to request a meeting to review and discuss Fisons promotional plans and materials.
January 24, 1992	Submission of comparative bioavailability data of Tilade Inhaler and nedocromil sodium nasal solution, as requested by Dr. Sherwin Straus, Medical Officer (FDA).
January 27, 1992	Submission to Docket No. 87P-0422/CP of a separate environmental assessment report covering the use of chlorofluorocarbons with the citizen petition.
January 27, 1992	Amendment to the environmental assessment report to the NDA to update the information on the alternative USA sites for quality control testing.
February 3, 1992	Letter to the Division to notify of a clinical information amendment submitted under IND 21,544 for Tilade Inhaler on January 31, 1992.
February 12, 1992	Facsimile transmission to Dr. Alan Schroeder, Reviewing Chemist (FDA) of draft responses to the chemistry questions in the FDA letter of February 3, 1992.
February 13, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of a copy of the January 6, 1992 submission which discussed the safety profile of Tilade Inhaler and included a correction to the Adverse Events table from the draft package circular, as requested by Mr. Joseph Buccine on February 12, 1992.
February 14, 1992	Submission to respond to the FDA letter of February 3, 1992 which contained questions on the November 27, 1991 and December 31, 1991 chemistry, manufacturing and control amendments.
March 24, 1992	Letter to the Division responding to the February 12, 1992 communication from the Division which contained comments from the CDER CAC. Attached was a draft outline protocol for a study to obtain dietary pharmacokinetic data.

Date	Description
March 31, 1992	Submission to update the methods validation package submitted on December 31, 1991 as requested in the FDA letter of February 3, 1992.
April 3, 1992	Submission to provide three copies of the March 31, 1992 submission which were inadvertently omitted.
April 3, 1992	Submission to provide further information and background regarding the calculations which were used to determine the proposed maximum allowable concentrations of various extractants from the elastomers present in the valve, as requested by Dr. Alan Taylor, Supervisory Pharmacologist, (FDA) on March 12, 1990.
April 17, 1992	Submission to correct the methods validation package submitted on March 31, 1992 to include revised specifications as submitted on February 14, 1992.
April 17, 1992	Letter to the Division requesting clarification and rationale for the request to delete references to nedocromil sodium being an anti-inflammatory agent from the draft package circular.
May 6, 1992	Submission to the Division withdrawing the Rochester, NY facility as a testing site for Tilade Inhaler under NDA 19-660. Included were an updated QC Protocol of System and Environmental Assessment Report.
May 7, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of a copy of the cover letter to the May 6, 1992 submission.
May 8, 1992	Submission to Docket No. 87P-0422/CP to update the Environmental Assessment Report to delete the Rochester, NY facility as a site for quality control testing.
May 22, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of a list of safety related submissions made to IND 21,544 since January 6, 1992, as requested by Mr. Joseph Buccine.
May 28, 1992	Letter to the Division to provide data on extractables with Intal Inhaler at the end of its shelf life, as requested by Dr. Alan Taylor, Supervisory Pharmacologist (FDA).
June 3, 1992	Amendment to provide additional information on the spray pattern test, in conjunction with the amendments of August 20, 1991, November 27, 1991 and December 31, 1991.
June 11, 1991	Letter to the Division to notify of an amendment to IND 21,544 for Tilade Inhaler of pharmacology/toxicology and clinical information.

Date	Description
June 18, 1992	A copy of excerpts from the Standard Operating Procedure for performing histology on rat lungs and respiratory tract, as requested by Dr. Alan Taylor, Supervisory Pharmacologist (FDA).
June 30, 1992	Further details concerning histology procedures on the rat larynx, as requested by Dr. Alan Taylor, Supervisory Pharmacologist (FDA).
June 30, 1992	Amendment of results on an improved can pressure test to make it more accurate and precise and a repeated temperature cycling study evaluating the potential effects on particle size distribution.
July 10, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of an chronology of safety related submissions to update those submitted January 6, 1992 and May 22, 1992.
July 10, 1992	Submission of a document concerning the anti-inflammatory activity of nedocromil sodium to support the classification of nedocromil sodium as an anti-inflammatory agent.
July 14, 1992	Letter to the Division to request a meeting to discuss Fisons' development plans of non-CFC products.
July 15, 1992	Various information submitted: 1) Listing of all safety related submissions to IND 21,544 and NDA 19-660 2) Proposed wording to describe the Onset of Action of nedocromil sodium in the draft package circular 3) A revised adverse reactions table and text for the draft package circular 4) A review of ADR and patient deaths since the October 15, 1990 submission
July 16, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of the bibliography page inadvertently omitted from the July 10, 1992 submission, as requested by Mr. Joseph Buccine.
July 17, 1992	Various information submitted: 1) Revised draft pediatric page from the FDA version sent on July 8, 1992 2) Updated Summary Basis of Approval 3) Correction to Adverse Reactions Text submitted on July 15, 1992 4) Two complete copies of the document submitted on July 10, 1992

Date	Description
July 22, 1992	Various information submitted: 1) Final proposed language for the pediatric page 2) Additional language proposed for the onset of action for the draft package circular 3) Addition of the adverse event: warmth
August 4, 1992	Submission of case report forms for Patient LQ05 from Study No. 84-754 and Patient 35 from 87-30, and information on a case of fatal status asthmaticus, as requested by Mr. Joseph Buccine, CSO (FDA).
August 6, 1992	Letter to the Division confirming agreement to the list of commitments in the FDA letter of July 27, 1992.
August 10, 1992	Submission of a Case Report Form for Patient 110 from Study 904, as requested by Mr. Joseph Buccine, CSO (FDA).
August 14, 1992	Information on the synthesis of intermediate FPL 60518XX, allyloxybisethanone, as requested by Dr. Guiragos Poochikian, Chemistry Reviewer (FDA).
August 17, 1992	Facsimile transmission to Mr. Joseph Buccine, CSO (FDA) of a copy of the language for the carcinogenicity section of the package circular sent to Dr. Alan Taylor on October 9, 1991 and a copy of the facsimile sent to Joseph Buccine on December 6, 1991 confirming acceptability of this language, and the wording relative to maintenance therapy which was deleted from the Division's August 12, 1992 version of draft labeling.
September 1, 1992	Amendment proposing tightened related substances limits for allyloxybisethanone synthesized by Route 1 to fulfill a commitment made on August 13, 1992.
November 5, 1992	Facsimile transmission and submission to Dr. Tunda Otulana, Medical Reviewer (FDA) of the document entitled "Proposed Clinical Studies for Alternative Propellant Registration."
November 6, 1992	Letter to Mr. Joseph Buccine, CSO, outlining labeling issues Fisons feels are critical to resolve prior to approval of the NDA.
November 20, 1992	Submission of revised draft labeling of the package circular and patient instructions in response to the November 16, 1992 facsimile from the Division and various telephone communications between Mr. Joseph Buccine, CSO (FDA) and Dr. Robert Parker, Fisons.

Date	Description
November 30, 1992	Submission of Final draft labeling of the package circular, patient instructions and container/pack labeling in response to the November 25, 1992 telephone communication between Mr. Joseph Buccine, CSO (FDA) and Dr. Robert Parker, Fisons.

APPENDIX 7

Certified copy of the application papers

CERTIFICATION

The undersigned hereby certifies that attached hereto is a true copy (except with respect to the handwritten changes and additions, which did not appear on the original) of the application papers filed in patent application Serial No. 06/344,983 which issued as U.S. Patent 4,474,787.

Basil P. Mann
Registration No. 18,464

42493

JOINT INVENTORS

APPLICATION FOR
UNITED STATES LETTERS PATENT

SPECIFICATION

TO ALL WHOM IT MAY CONCERN:

Be it known that we, HUGH CAIRNS

a citizen of the United ~~States~~, residing at Kingdom of Great Britain & Northern Ireland 2 Oxburgh Close, Thorpe Acre,

in the County of Leicestershire and State of England

and DAVID COX

a citizen of the United ~~States~~, residing at Kingdom of Great Britain & Northern Ireland 60 Atherstone Road, Loughborough

in the County of Leicestershire and State of England

and

a citizen of the United States, residing at

in the County of and State of

and

a citizen of the United States, residing at

in the County of and State of

have invented a new and useful "COMPOUNDS"

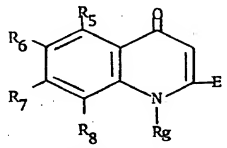
of which the following is a specification.

BA 18597/77

COMPOUNDS

ABSTRACT

There are described compounds of formula I



I

in which an adjacent pair of R_5, R_6, R_7 and R_8 form a chain -COCH=CE-O-, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and

E is -COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable derivatives thereof.

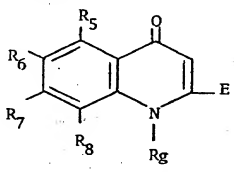
There are also described processes for making the compounds and pharmaceutical, e.g. anti-allergic, compositions containing the compounds.

This application is a continuation in part of our co-pending application Serial No. 897,416 filed April 18, 1978.

BA 18957/77

This invention relates to new pyranoquinolinone derivatives, compositions containing them and methods for their preparation.

According to our invention we provide compounds of formula I,



I

in which an adjacent pair of R_5, R_6, R_7 and R_8 form a chain -COCH=CE-O-, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

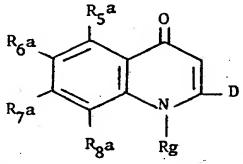
Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and

E is -COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable derivatives thereof.

According to our invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable derivative thereof, which comprises,

(a) producing a compound of formula I in which E is -COOH by selectively hydrolysing or oxidising a compound of formula II,



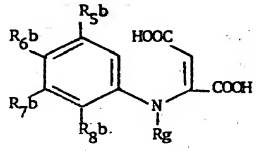
II

in which Rg is as defined above,

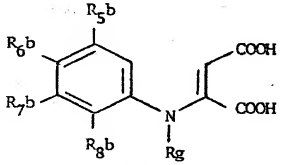
R_5a, R_6a, R_7a and R_8a have the same significances as R_5, R_6, R_7 and R_8 above, save than an adjacent pair of R_5a, R_6a, R_7a and R_8a may represent a chain of formula $-COCH=C(D_1)O-$, and

one or both of D and D_1 represents a group hydrolysable or oxidisable to a -COOH group, and the other may represent a -COOH group,

(b) producing a compound of formula I in which E is -COOH by cyclising a compound of formula III or IV,



III



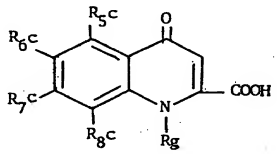
IV

or an ester of either thereof,

in which Rg is as defined above,

R_5b, R_6b, R_7b and R_8b have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5b, R_6b, R_7b and R_8b may represent the pair of groups -H and -O-C(COOH)=CH-COOH,

(c) producing a compound of formula I in which E is -COOH by cyclising a compound of formula V,



V

or an ester thereof,

in which Rg is as defined above,

R_5c, R_6c, R_7c and R_8c have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_5c, R_6c, R_7c and R_8c, instead of forming a chain -COCH=C(COOH)-O-, represent the pairs of groups:

(i) $-COCH_2CO-COR''$ or $-COCH=C(COOH)-NL_1L_2$, or a suitable derivative thereof; and -OM or a halogen atom, or

(ii) -H and -O-C(COR")=CH-COR"

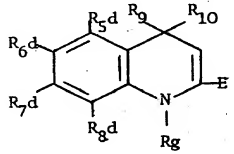
R" represents -OM, or a group which is hydrolysable thereto,

L_1 and L_2 which may be the same or different are each hydrogen, aryl or alkyl, or together form a saturated or unsaturated alkylene chain, and

M represents hydrogen or an alkali metal,

and if necessary or desired hydrolysing the group -COR'', to a group -COOM,

(d) conversion of a compound of formula VI,



VI

or an ester thereof,

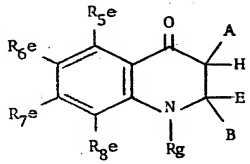
in which Rg and E are as defined above,

R_5d, R_6d, R_7d and R_8d have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_5d, R_6d, R_7d and R_8d may represent the chain $-C(R_9R_{10})=CE-O-$,

at least one of the pairs of groups R_9 and R_{10} together form a =S or together form an $-S(CH_2)_nS-$ chain in which n is 2 or 3, and the other pair R_9, R_{10} may represent =O,

to a corresponding compound of formula I,

(e) selectively removing the groups A and B from a compound of formula VII,



VII

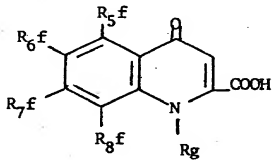
or an ester thereof,

in which Rg and E are as defined above,

R_5e, R_6e, R_7e and R_8e have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_5e, R_6e, R_7e and R_8e may represent a chain -COCHA-CBE-O-,

in at least one of the pairs of groups A and B both A and B are hydrogen, or one of A and B is hydrogen and the other is halogen or hydroxy, and the other pair A, B may together form a double bond,

(f) producing a compound of formula I in which E is -COOH by cyclising a compound of formula VIII,



VIII

or an ester thereof,

in which Rg is as defined above, R_5f, R_6f, R_7f and R_8f have the same significances as R_5, R_6, R_7 and R_8 above save that an adjacent pair of R_5f, R_6f, R_7f and R_8f, instead of forming a chain -COCH=C(COOH)-O-, represent the pair of groups -COCH(SOR_{10})-CH(OH)-COOR" and -OM,

R" and M are as defined above, and

R_{10} represents an alkyl C 1 to 10 group,

(g) producing a compound of formula I in which E is a 5-tetrazolyl group by reacting a corresponding compound of formula I in which E is -CN,

with an azide in a solvent which is inert under the reaction conditions, or

(h) producing a compound of formula I in which E is an (N-tetrazol-5-yl)carboxamido group by reacting a corresponding compound of formula I in which E is -COOH, or an acid halide, ester or mixed anhydride thereof,

with 5-aminotetrazole,

and if necessary or desired hydrolysing the ester of the compound of formula I and/or converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

In process (a) the group D may be, for example an ester, acid halide, amide or a nitrile group, which may be hydrolysed to a -COOH group. The hydrolysis may be carried out using conventional techniques, for example under mildly basic conditions, e.g. using sodium carbonate, sodium hydroxide, sodium bicarbonate, or under acidic conditions, e.g. a mixture of aqueous dioxan and hydrochloric acid, or hydrogen bromide in acetic acid. The hydrolysis may be carried out at a temperature of from about 25° to 120°C depending on the compounds used. Alternatively the group D may be an alkyl, e.g. a lower alkyl such as methyl, a hydroxymethyl, an aralkenyl, e.g. styryl, an acyl, e.g. a lower alkanoyl such as acetyl, or a formyl group. The oxidation may be carried out using conventional techniques which do not otherwise modify the molecule to such an extent that the yield of the desired product is uneconomical, for example an

alkyl or a hydroxymethyl group may be oxidised using selenium dioxide, e.g. under reflux in aqueous dioxan; or chromic acid, e.g. under reflux in aqueous acetic acid. Aralkenyl groups may be oxidised using, for example neutral or alkaline potassium permanganate in aqueous ethanol, and acyl groups may be oxidised using, for example chromic acid or an aqueous hypochlorite, e.g. sodium hypochlorite. The formyl group may be oxidised using, for example chromic acid or silver oxide.

In process (b) the cyclisation may be carried out by treating the compound of formula III or IV, with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, sulphuric or polyphosphoric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of from about 25° to 150°, and preferably from 75° to 150°C. We have found that isomerisation of the maleic acid derivative of formula IV to the corresponding fumaric acid derivative of formula III takes place when polyphosphoric acid is used to cyclise these compounds to a compound of formula I, thus enabling a satisfactory yield of the compound of formula I to be obtained from a prima facie unsatisfactory mixture of compounds of formulae III and IV. Compounds of formula III may also be cyclised by subjecting the compound to an elevated temperature, e.g. of from 200 to 250°C, optionally in the presence of a high boiling solvent which is inert under the reaction conditions, e.g. diphenyl ether.

When one of the groups is -OM the cyclisation of process

(c)(i) may be carried out by heating, or under basic or neutral conditions. It is however preferred to carry out the cyclisation in the presence of an acid, e.g hydrochloric acid, and in a solvent which is inert under the reaction conditions, e.g ethanol. The reaction may be carried out at from about 20° to 150°C. The group -COR'' is preferably an ester group, e.g R'' may be a lower alkoxy group. When one of the groups is $-COCH=C(COOH)-NL_1L_2$ the derivative of the -COOH group may be a group $-CONL_1L_2$ in which L_1 and L_2 are as defined above. It is preferred that L_1 and L_2 are hydrogen, phenyl, alkyl C 1 to 6 or together form a 4 or 5 membered alkylene chain, e.g. together with the nitrogen atom form a piperidine ring. When one of the groups is halogen the cyclisation may be carried out in a solvent which is inert under the reaction conditions, preferably a high boiling polar solvent, e.g pyridine, dimethylformamide or hexamethylphosphoramide. The reaction is preferably carried out with the aid of a strong base, for example an alkali metal hydride, e.g sodium hydride. The reaction is preferably carried out at a temperature of from about 80° to 200°C, in the absence of free oxygen, e.g under an inert atmosphere such as nitrogen.

The cyclisation of process (c)(ii) may be carried out by treating the compound of formula V with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, polyphosphoric or sulphuric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of

from 0° to 100°C. Alternatively cyclisation may be achieved by converting the free carboxy groups of the compound of formula V to acyl halide groups and subjecting the resulting acyl halide to an intramolecular Friedel-Crafts reaction.

In processes (d), when R_9 and R_{10} together form a chain -S-$(CH_2)_n$-S-, the conversion may comprise oxidative hydrolysis and may be carried out in an aqueous polar organic solvent, for example aqueous ethanol, acetone or tetrahydrofuran. The oxidative hydrolysis may be carried out in the presence of an oxidising agent, for example mercuric chloride, an N-halosuccinimide such as N-bromo- or N-chloro-succinimide, a per-acid such as periodic acid; or p-toluenesulphonchloramide or a salt thereof. When mercuric chloride is used the reaction may be carried out in the presence of a base, e.g. mercuric oxide, cadmium carbonate or calcium carbonate. N-halosuccinimides may be used alone or in the presence of a silver salt, e.g. silver perchlorate, or silver nitrate. The reaction may conveniently be carried out at a temperature of from about 15° to 100°C.

When R_9 and R_{10} together form a =S group the conversion may comprise (oxidative) hydrolysis and may be carried out in the presence of a heavy metal compound, e.g. a compound of group Ib, IIb or IIIb of the Periodic Table of Mendeleef, as catalyst. Suitable compounds include mercury, thallium and silver compounds, e.g. mercury (II) acetate or chloride, thallium (III) trifluoroacetate, or silver oxide. The reaction may be carried out in the

presence of water and an organic solvent system such as acetone-acetic acid, alkanols, tetrahydrofuran/methanol, or tetrahydrofuran. Alternatively the reaction may be carried out by alkylation followed by hydrolysis. In such cases the reaction may be effected by (i) an alkyl halide or sulphonate (e.g. methyl iodide), in a moist solvent, e.g. acetone, (ii) an alkylfluorosulphonate and water in sulphur dioxide, or (iii) a trialkyl oxonium fluoroborate followed by aqueous sodium hydroxide.

When both A and B are hydrogen process (e) is a dehydrogenation and may be carried out by oxidation using a mild oxidising agent, for example selenium dioxide, palladium black, chloranil, lead tetraacetate or triphenyl methyl perchlorate. Alternatively the dehydrogenation of a compound of formula VII in which both A and B are hydrogen may be carried out indirectly by halogenation followed by dehydrohalogenation, e.g. by treatment with N-bromosuccinimide or pyridinium bromide perbromide to yield a compound of formula VII in which A is halogen and B is hydrogen, which is subsequently dehydrobrominated. When one of A and B is hydroxy the dehydration may be catalysed by an acid, e.g. sulphuric or oxalic acid; a base, e.g. potassium hydroxide; or a salt, e.g. potassium hydrogen sulphate; or N-bromosuccinimide. The reaction may be carried out in a solvent which is inert under the reaction conditions, e.g. a halogenated hydrocarbon, xylene, or glacial acetic acid. The reaction may be carried out at an elevated temperature, e.g. from 20 to 150°C.

The cyclisation of process (f) may be carried out in a solvent which is inert under the reaction conditions, e.g. diethyl ether or benzene. The reaction may also, if desired, be carried out in the presence of a Lewis acid, e.g. boron trifluoride. The reaction is preferably carried out at a temperature of from 10 to 120°C in presence of an organic base, e.g. piperidene.

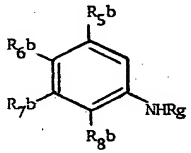
Suitable solvents which are inert under the reaction conditions of process (g) include those in which both the reagents are soluble, e.g. N,N-dimethylformamide. Other solvents which may be mentioned include dimethylsulphoxide, tetrahydrofuran, diethyl glycol and ethyl methyl glycol. The reaction is preferably carried out at a temperature of from about 20° to 130°C for from about 1 to 20 hours. The azide used in the reaction is preferably ammonium or an alkali metal azide, e.g. sodium or lithium azide, but other azides, e.g. aluminium azide or the azides of nitrogen containing bases, e.g. mono-, di-, tri-, and tetra- methyl- ammonium, anilinium, morpholinium and piperidinium azides, may also be used if desired. Where an azide other than that of an alkali metal is used this azide may be prepared in the reaction mixture by double decomposition. The reaction may, if desired, be carried out in the presence of an electron acceptor, e.g. aluminium chloride, boron trifluoride, ethyl sulphonic acid or benzene sulphonic acid. As an alternative to the reaction conditions set out above, the reaction may be carried out using hydrazoic acid (hydrogen azide) at a temperature

of from about 20° to 150°C in a suitable solvent, under greater than atmospheric pressure. When an azide other than hydrazoic acid is used, e.g. sodium azide, the product of the reaction will be the corresponding tetrazole salt. This salt may readily be converted to the free acid by treatment with strong acid, e.g. hydrochloric acid.

In process (h) the anhydride is preferably a mixed anhydride of such a type that it will cleave preferentially, to give the desired chromone carboxamidotetrazole, as the major product when reacted with the 5-aminotetrazole. Examples of suitable acids from which the mixed anhydride may be derived are sulphonic acids e.g. benzene sulphonic acid, sterically hindered carboxylic acids, e.g. pivalic, isovaleric, diethylacetic or triphenylacetic acid, and alkoxy formic acids, e.g. a lower alkoxy formic acid such as ethoxy or isobutoxy formic acid. When an acid halide is used it may conveniently be an acid chloride. The reaction is preferably carried out under anhydrous conditions in a solvent which will not react with either the 5-aminotetrazole or the mixed anhydride or acid halide, e.g. pyridine or dimethylformamide. However when the reaction is carried out in a non-basic solvent, e.g. dimethylformamide, an adequate proportion of an acid acceptor, e.g. triethylamine, should also preferably be present. The reaction is preferably carried out at a temperature of from about -15° to +20°C. When an ester is used we prefer to use a lower alkoxy ester and to carry out the reaction in a solvent

which is inert under the reaction conditions, e.g. glacial acetic acid, at a temperature of from about 100 to 150°C. When a compound of formula I in which E is -COOH is used as starting material the reaction may be carried out by heating the compound of formula I and the 5-aminotetrazole in a solvent which is inert under the reaction conditions, e.g. dimethylacetamide, at a temperature of from 100 to 200°C. Alternatively the reaction may be carried out in the presence of a condensation agent, e.g. N,N'-carbonyl-diimidazole or dicyclohexyl carbodiimide, in an aprotic solvent, e.g. dimethylformamide, at a temperature of from about 10 to 40°C.

The starting materials for process (b) may be made by reacting a compound of formula IX,



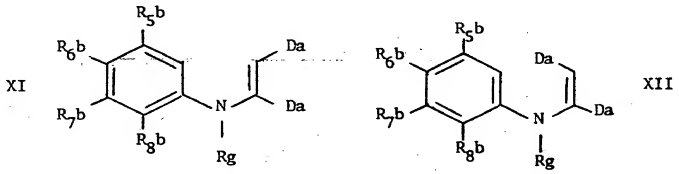
IX

in which Rg, R_5b, R_6b, R_7b and R_8b are as defined above, with a compound of formula X,

$$Da\text{-}C\equiv C\text{-}Da \qquad X$$

in which Da is an ester group,

to produce a mixture of compounds of formulae XI and XII,



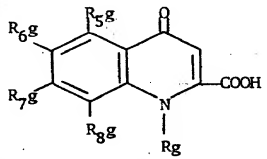
XI XII

in which Rg, Da, R_5b, R_6b, R_7b and R_8b are as defined above.

The compounds of formula XI and XII may be hydrolysed to give compounds of formulae IV and III. Alternatively the groups Da in the compounds of formulae XI and XII may be converted using conventional techniques known per se, to other groups D and the resulting compounds cyclised, using the same conditions as for process (b) above, to yield a compound of formula II. As a further and preferred alternative the compounds of formula XI and XII may be cyclised, using the same conditions as for process (b) above, to give a compound of formula II in which D is an ester group, and the resulting compound of formula II is used itself in process (a), or the D group converted to another group D, e.g an acid halide, amide or nitrile group, using techniques known per se.

The fumarate isomer of formula XII (or the corresponding compound in which Da has been converted to D) is the only isomer which can cyclise to give the required compounds of formula II. The proportion of the two isomers may be readily determined by nuclear magnetic resonnance spectroscopy and we have found that, in general, the desired fumaric acid derivative is only a minor proportion of the mixture of isomers obtained from the reaction.

The compounds of formula V, in which an adjacent pair of R_5c, R_6c, R_7c and R_8c represent the groups $-COCH_2COCR''$ and -OM or halogen, may be made by reacting a compound of formula XIII,



XIII

or an ester thereof,

in which Rg is as defined above,

and R_5g, R_6g, R_7g and R_8g have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5g, R_6g, R_7g and R_8g, instead of forming a $-COCH=CH(COOH)-O-$ chain, represent the groups $-COCH_3$ and -OM or halogen, in which M is as defined above,

with a compound of formula XIV,

$$R'CZ-CZR'' \qquad \text{XIV}$$

in which R'' is as defined above,

R' is a suitable leaving group, e.g an alkoxy, halo, amino, alkylamino, substituted amino (e.g an arylsulphonylamino group) or substituted alkylamino group, reactive with the carbanion of the $-COCH_3$ group of the compound of formula XIII, and

each Z is a carbonyl oxygen atom, or one Z may represent two halogen atoms and the other a carbonyl oxygen atom,

and if necessary hydrolysing the resulting compound to a

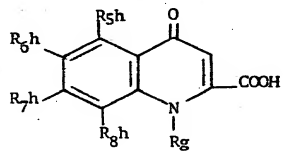
compound of formula V. The preferred compounds of formula XIV are dialkyl oxalates, e.g diethyl oxalate.

Compounds of formula V bearing a $-COCH=C(COOH)-NL_1L_2$ group, or a derivative thereof, may be made from known compounds in one or more steps using processes known per se.

The compounds of formula II may be made as described above or by a process analogous to process (c)(i).

Alternatively the compounds of formula II may, for example in the case of the acid halide, the amide and the nitrile, be made from compounds of formula I using conventional techniques, e.g reaction of an ester of the compound of formula I with ammonia to produce the amide, followed by dehydration of the amide to form the nitrile.

The compounds of formula V carrying substituents -H and $-O-C(COR'')=CH-COR''$ may be made by reacting a compound of formula XV,



XV

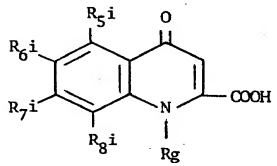
or an ester thereof,

in which Rg is as defined above, and R_5h, R_6h, R_7h and R_8h have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5h, R_6h, R_7h and R_8h, instead of forming a $-COCH=C(COOH)-O-$ chain,

represent the groups -H and -OH,

with a dialkyl acetylene dicarboxylate, in conventional manner, followed if necessary by hydrolysis of the reaction product.

Compounds of formula VIII may be made by reacting a compound of formula XVI,



XVI

or an ester thereof,

in which Rg is as defined above,

R_5i, R_6i, R_7i and R_8i have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5i, R_6i, R_7i and R_8i, instead of forming a chain -COCH=C(COOH)-O-, represent the pair of groups -OH and -COO-Alkyl,

with a methyl alkyl sulphoxide anion, e.g. the anion of dimethyl sulphoxide,

and reacting the resulting o-hydroxy-2-alkylsulphinyl compound with glyoxalic acid or an ester thereof.

The compounds of formula I in which E is -CN may be made by dehydrating the corresponding pyranoquinolinone amide using, for example, phosphorus oxychloride, as dehydrating agent. The reaction is preferably carried out using at least one molar equivalent of

dehydrating agent per mole of the pyranoquinolinone amide. Where the dehydrating agent reacts with one of R_5, R_6, R_7 or R_8 (e.g. a substituent comprising an -OH group) sufficient dehydrating agent should be used to satisfy the side reaction as well as the main reaction. The reaction may, if desired, be carried out in the presence of an acid binding agent, e.g. triethylamine. The reaction may be carried out in the presence of a solvent, e.g. N,N-dimethylformamide, dimethyl sulphoxide, pyridine, benzene or hexamethyl phosphoramide, or an excess of the dehydrating agent may be used as the reaction medium. The reaction may be carried out at a temperature of from about 0° to 200°C depending on the dehydrating agent used. When phosphorus oxychloride is used a temperature of from 0° to 100°C is preferred.

The chromone amide starting materials may be made by reacting a corresponding pyranoquinolinone ester with ammonia, using techniques conventional in the production of amides from esters, e.g. using an alkanol as solvent at a temperature of 0° to 120°C.

Compounds of formulae VI, VII, IX, XIII, XIV, XV and XVI are either known or may be made from known compounds using conventional techniques known per se.

The processes as described above may produce the compound of formula I or a derivative thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

The compounds of formula I and the intermediates therefore may be isolated from their reaction mixtures using conventional techniques.

Pharmaceutically acceptable derivatives of the compounds of formula I include pharmaceutically acceptable salts, and when E is a -COOH group, esters and amides of the 2-carboxylic acid group. Suitable salts include ammonium, alkali metal (e.g sodium, potassium and lithium) and alkaline earth metal (e.g. calcium or magnesium) salts, and salts with suitable organic bases, e.g. salts with hydroxylamine, lower alkylamines such as methylamine or ethylamine, with substituted lower alkylamines, e.g hydroxy substituted alkylamines such as tris(hydroxymethyl)methylamine, or with simple monocyclic nitrogen heterocyclic compounds, e.g piperidine or morpholine. Suitable esters include simple lower alkyl esters, e.g the ethyl ester, esters derived from alcohols containing basic groups, e.g di-lower alkyl amino substituted alkanols such as the β-(diethylamino)-ethyl ester, and acyloxy alkyl esters, e.g a lower acyloxy-lower alkyl ester such as the pivaloyloxymethyl ester, or a bis-ester derived from a di-hydroxy compound, e.g a di(hydroxy-lower alkyl) ether, e.g the bis-2-oxapropan-1,3-diyl ester. The pharmaceutically acceptable acid addition salts of the basic esters, and also of those compounds in which one of R_5, R_6, R_7 and R_8 is a group $-NR_1R_2$, e.g the hydrochloride, the hydrobromide, the oxalate, the maleate or the fumarate salts, may also be used. The esters may be made by conventional techniques, e.g esterification or

transesterification. The amides may be, for example, unsubstituted or mono- or di- C 1 to 6 alkyl amides and may be made by conventional techniques, e.g reaction of an ester of the corresponding acid with ammonia or an appropriate amine.

The compounds of formula I and pharmaceutically acceptable derivatives thereof are useful because they possess pharmacological activity in animals; in particular they are useful because they inhibit the release and/or action of pharmacological mediators which result from the in vivo combination of certain types of antibody and specific antigen, e.g the combination of reaginic antibody with specific antigen (see Example 27 of British Patent Specification No 1,292,601). The new compounds have also been found to interfere with reflex pathways in experimental animals and man and in particular those reflexes associated with lung function. In man, both subjective and objective changes which result from the inhalation of specific antigen by sensitised subjects are inhibited by prior administration of the new compounds. Thus the new compounds are indicated for use in the treatment of reversable airway obstruction and/or to prevent the secretion of excess mucous. The new compounds are thus indicated for the treatment of allergic asthma, so-called 'intrinsic' asthma (in which no sensitivity to extrinsic antigen can be demonstrated), bronchitis, coughs and the nasal and bronchial obstructions associated with the common colds. The new compounds may also be of value in the treatment of other conditions in which antigen-antibody reactions or

excess mucous secretion are responsible for, or are an adjunct to, disease, for example, hay fever; certain eye conditions, e.g trachoma; alimentary allergy, e.g urticaria and atopic eczema; and gastrointestinal conditions, for example gastrointestinal allergy, especially in children, e.g milk allergy, or ulcerative colitis.

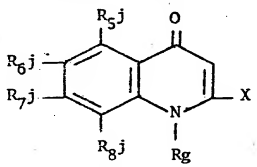
For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 0.001 to 50 mg per kg of animal body weight in the test set out in Example 27 of British Patent Specification No 1,292,601. For man the indicated total daily dosage is in the range of from 0.01 mg to 1,000 mg preferably from 0.01 mg to 200 mg and more preferably from 1 mg to 60 mg, which may be administered in divided doses from 1 to 6 times a day or in sustained release form. Thus unit dosage forms suitable for administration (by inhalation or oesophageally) comprise from 0.01 mg to 50 mg, preferably 0.01 mg to 20 mg and more preferably from 0.01 mg to 10 mg of the compound preferably admixed with a solid or liquid pharmaceutically acceptable diluent, carrier or adjuvant.

The compounds of formula I, and pharmaceutically acceptable derivatives thereof, have the advantage that they are more efficacious in certain pharmacological models, or are longer acting than compounds of similar structure to the compounds of

formula I. Furthermore the compounds of formula I, and pharmaceutically acceptable derivatives thereof, are advantageous in that they are more efficaceous in interfering with reflex pathways and in inhibiting the secretion of mucous than are compounds of similar structure to the compounds of formula I.

We prefer each of Rg, R_5, R_6, R_7 and R_8, when they contain carbon, to contain up to 8, and preferably up to 4 carbon atoms. Specifically we prefer R_5, R_6, R_7 and R_8 to be selected from hydrogen, methoxy, propyl, allyl, methyl, ethyl, chlorine, bromine and hydroxy. The -COCH=CE-O- chain may be bonded to the benzene ring in any sense and in any of the adjacent positions R_5, R_6, R_7, R_8. However, we prefer the chain to be bonded in the positions R_6 and R_7 the -O- part of the chain being in position R_7. We also prefer the group E to be a -COOH group.

According to the invention there is also provided a process for the production of a pharmaceutically acceptable salt of a compound of formula I, which comprises treating a compound of formula Ic,



Ic

in which Rg is as defined above,

R_5j, R_6j, R_7j and R_8j have the same significances as R_5, R_6, R_7 and R_8 above, save that an adjacent pair of R_5j, R_6j, R_7j and

R_8j may form a chain -O-C(X)=CHCO-, and

X is a 5-tetrazolyl group, an (N-tetrazol-5-yl)carboxamido group, a carboxylic acid group (or an ester thereof, or another salt thereof), a nitrile group, an acid halide group or an amide group,

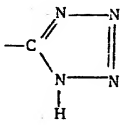
with a compound containing an available pharmaceutically acceptable cation and capable of converting the group X to a pharmaceutically acceptable salt of an E group.

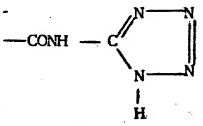
Compounds capable of converting the group X to a pharmaceutically acceptable salt of an E group include compounds, e.g bases and ion exchange resins, containing pharmaceutically acceptable cations, e.g sodium, potassium, calcium, ammonium and appropriate nitrogen containing organic cations. In general we prefer to form the pharmaceutically acceptable salt by treating the free acid of formula I with an appropriate base, e.g with an alkaline-earth or alkali metal hydroxide, carbonate or bicarbonate in aqueous solution or by a metathetical process with an appropriate salt. When a strongly basic compound is used care should be taken, e.g by keeping the temperature sufficiently low, to ensure that the compound of formula I is not hydrolysed or otherwise degraded. The pharmaceutically acceptable salt may be recovered from the reaction mixture by, for example, solvent precipitation and/or removal of the solvent by evaporation, e.g by freeze drying.

According to our invention we also provide a pharmaceutical

composition comprising (preferably less than 80%, and more preferably less than 50% by weight) of a compound of formula I, or a pharmaceutically acceptable derivative thereof, in combination with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of suitable adjuvants, diluents or carriers are:- for tablets capsules and dragées; microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin; for suppositories, natural or hardened oils or waxes; and for inhalation compositions, coarse lactose. The compound of formula I, or the pharmaceutically acceptable derivative thereof, preferably is in a form having a mass median diameter of from 0.01 to 10 microns. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilizers, sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form. We prefer compositions which are designed to be taken oesophageally and to release their contents in the gastrointestinal tract.

The 5-tetrazolyl and (N-tetrazol-5-yl)carboxamido groups are of formulae XVII and XVIII respectively,

XVII 

 XVIII

The groups of formulae XVII and XVIII may exist in tautomeric forms and such tautomeric forms are included within the definition of the compounds of formula I.

The invention is illustrated, but in no way limited by the following Examples.

Example 1

4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(a) 4-Acetamido-2-allyloxyacetophenone

4-Acetamido-2-hydroxyacetophenone (19.3g) allyl bromide (12.1 ml) and anhydrous potassium carbonate (21.5g) were stirred in dry dimethylformamide (250 ml) at room temperature for 24 hours. The reaction mixture was poured into water and the product was extracted with ethyl acetate. The organic solution was then washed well with water dried over magnesium sulphate and evaporated to dryness. The sub-title product was obtained as buff coloured solid (20.5g). The structure of the product was confirmed by NMR and mass spectroscopy.

(b) 4-Acetamido-3-allyl-2-hydroxyacetophenone

The above allyl ether (18.4g) was heated at 200-210°C for 4 hours. 17.1g of the thermally rearranged sub-title product was obtained as a brown solid. Again the structure was confirmed by NMR and mass spectroscopy.

(c) 4-Acetamido-2-hydroxy-3-propyl acetophenone

The product of step (b) (17g) was dissolved in glacial acetic acid and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through

a kieselguhr filter and the filtrate was evaporated to leave 13.0g of almost colourless solid. The mass and NMR spectra confirmed the structure of the product.

(d) Ethyl 7-acetamido-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A mixture of diethyl oxalate (19.3g; 17.9 ml) and the above product of step (c) (12.4g) in dry ethanol (100 ml) was added to a stirred solution of sodium ethoxide in ethanol (prepared by dissolving sodium (6.1g) in dry ethanol (200 ml)). The reaction mixture was refluxed for 3 hours and then poured into dilute hydrochloric acid and chloroform. The chloroform layer was separated, washed with water and dried. The solvent was evaporated to leave a brown solid which was dissolved in ethanol (300 ml) containing concentrated hydrochloric acid (3 ml) and the whole was refluxed for 1 hour. The reaction mixture was poured into water and the product was extracted into ethyl acetate which was washed with water and dried. The solvent was evaporated to leave 10 g of a sticky solid which had mass and NMR spectra consistent with the expected product.

(e) Ethyl 7-amino-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A solution of the amide of step (d) (10g) in ethanol (300 ml), containing concentrated hydrochloric acid (5 ml), was refluxed for 8 hours. The reaction mixture was diluted with water and extracted into ethyl acetate. The extract was washed with water, dried and the solvent was evaporated to leave a dark brown semi-solid. This was chromatographed on a silica gel column, using

ether as eluant to give 4.8g of the required product whose structure was confirmed by mass and NMR spectral evidence; mp 84-87°C.

(f) 8-Ethoxycarbonyl-2-methoxycarbonyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline

The amino benzopyran of step (e) (2.0g) and dimethyl acetylene dicarboxylate (1.24g; 1.01 ml) were refluxed in ethanol (30 ml) for 26 hours. The reaction mixture was cooled to 0°C and the insoluble yellow-brown solid was collected by filtration and washed with a little ethanol and dried to give 2.0g of a product which was a mixture of maleic and fumaric esters obtained by Michael addition of the amine to the acetylene.

This mixture of esters (2.0g) was treated with polyphosphoric acid (30 ml) and heated on the steam bath with stirring for 20 minutes. The reaction mixture was then poured onto ice and stirred with ethyl acetate. The organic layer was separated, washed with water and dried. The solvent was evaporated to leave 1.6g of a yellow orange solid. Recrystallisation of this solid from ethyl acetate gave the required product as fluffy orange needles mp 187-188°C.

Analysis

Found: C, 62.0%; H, 5.1%; H, 3.7%

$C_{20}H_{19}NO_7$ Required: C 62.3%; H, 4.9%; N, 3.6%

(g) 4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (2.5g) was refluxed with sodium bicarbonate

(1.64g) in ethanol (100 ml) and water (50 ml) for 1½ hours. The whole was poured into water and acidified to precipitate a gelatinous solid. This was collected by filtration, refluxed with ethanol and the product was separated by centrifugation (1.4g) mp 303-304°C dec. The structure of the product was confirmed by mass and NMR evidence.

(h) Disodium 4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The bis acid from step (g) (1.35g) and sodium bicarbonate (0.661g) in water (150 ml) were warmed and stirred until a clear solution was obtained. This solution was filtered and the filtrate was freeze dried to give 1.43g of the required disodium salt.

Analysis

Found: C, 46.1%; H, 4.0%; N, 2.9%

$C_{17}H_{11}NO_7Na_2$ 12.5% H_2O required: C, 46.1%; H, 3.8%; N, 3.15%

Example 2

4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(a) 4-(N-Acetyl-N-ethyl)amino-2-allyloxyacetophenone

4-(N-acetyl-N-ethyl)amino-2-hydroxyacetophenone (92.6g), allyl bromide (51 mls) and anhydrous potassium carbonate (90.4g) were stirred in dry dimethylformamide (500 mls) for 17 hours. The reaction mixture was poured into water and the product was extracted with ether. The organic solution was then washed well with water, dried over magnesium sulphate and evaporated to

dryness. The product was obtained as an oil (102.5g). The structure of the product was confirmed by NMR and mass spectroscopy.

(b) 4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone

The allyl ether product of step (a) (100.5g) was refluxed in diethylaniline (300 mls) for 3 hours. The reaction mixture was cooled and poured into dilute hydrochloric acid and extracted into ether, which latter was washed with dilute hydrochloric acid, and then with water. The organic solution was extracted with 10% sodium hydroxide solution which was then acidified. The precipitated product was extracted with ether which was dried over magnesium sulphate. The resulting ethereal solution was evaporated to dryness to give a yellow-brown oil (78.7g). This oil was a mixture of 4-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone and 6-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone.

This mixture was dissolved in ethanol (500 mls) and glacial acetic acid (20 mls) and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through kieselguhr and the filtrate evaporated to leave 79.9g of brown oil. This brown oil was a mixture and was separated by high pressure liquid chromatography using ether/petroleum ether (1:1) as solvent to give 44.2g of the sub-title compound and 23.8g of 6-(N-acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone.

(c) 4-N-Ethylamino-3-propyl-2-hydroxyacetophenone

4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone (44g) was refluxed in 48% hydrogen bromide in glacial acetic acid (100 mls), glacial acetic acid (500 mls) and water (20 mls) for 6 hours. The reaction mixture was poured on to ice-water and extracted with ethyl acetate which was washed with water, sodium bicarbonate solution, then water again and dried over magnesium sulphate. The organic solvent was evaporated to dryness to leave the sub-title compound as a red oil (34g). The structure was confirmed by NMR and mass spectroscopy.

(d) Methyl 6-acetyl-1-ethyl-7-hydroxy-4-oxo-8-propyl-4H-quinoline-2-carboxylate

The amine product of step (c) (17g) and dimethacetylenedicarboxylate (11.3 mls) were refluxed in ethanol (300 mls) for 17 hrs. The reaction mixture was cooled and evaporated to dryness to leave a deep red oil. This oil was chromatographed on a silica gel column using ether/petroleum ether (1:1) as eluant to give 19.1g of dimethyl 1-(4-acetyl-3-hydroxy-2-propylphenyl)-N-ethylamino-maleate m.p. 83-87°C.

The maleic ester (5g) was heated and stirred in polyphosphoric acid (100 mls) on the steam bath for 10 minutes. The reaction mixture was cooled and poured on to a mixture of ice-water and ethyl acetate. The organic solution was separated, washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave a pale yellow solid. This

product was purified by high pressure liquid chromatography to give 2.6g of the sub title compound m.p. 121-123°C.

Analysis

Found: C: 65.5% H; 6.6% N; 4.2%

$C_{18}H_{21}NO_5$ Required: C: 65.3% H; 6.34% N; 4.23%

Methyl 6-acetyl-1-ethyl-5-hydroxy-4-oxo-4H-quinoline-2-carboxylate was obtained from the purification as a pale yellow solid (100 mgs).

(e) Diethyl 4,6-dioxo-1-ethyl-10-propyl-4H-6H-pyrano[3,2-g]-quinoline-2,8-dicarboxylate

The hydroxy ketone product of step (d) (1.0g) and diethyl oxalate (3.3 mls) in dry dimethylformamide (25 mls) were added to ether washed 50% sodium hydride (0.581g) in dry dimethylformamide (20 mls) and the reaction mixture stirred for 4 hours. The reaction mixture was then poured into water, acidified and extracted with ethyl acetate, which was then washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to give an oil which was dissolved in ethanol (100 mls) and concentrated hydrochloric acid (a few drops) added. The solution was refluxed for ½ hr, cooled, poured into water and extracted with ethyl acetate, which was washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave an oil which solidified on trituration with 40-60° petroleum ether (1.2g). The structure of the compound was confirmed by NMR.

(f) 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (1.0g) and sodium bicarbonate (0.787g) in ethanol (85 mls) and water (32 mls) were refluxed for 4 hours. The reaction mixture was poured into water, acidified and the precipitate was collected by filtration and dried. The product was purified by triturating with boiling ethanol, then twice with boiling acetone. After each trituration the mixture was centrifuged and the supernatent liquid was removed by decantation. The residual solid was dried to give 0.547g of the required di-acid as a yellow powder m.p. 298-300° dec.

Analysis: Found: C: 61.3% H; 5.0% N; 3.6%

$C_{19}H_{17}NO_7$ Required: C: 61.5% H; 4.6% N; 3.79%

(g) Disodium 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The above di-acid (4.098g), suspended in water (100 mls) and was treated with sodium bicarbonate (1.82g). The resulting solution was filtered and the filtrate was treated with acetone until complete precipitation of the product had occurred. The required di-sodium salt was filtered off and dried to give 3.39g of a pale yellow powder.

Analysis:

Found: C: 51.1% H; 4.3% N; 3.0%

$C_{19}H_{15}NNa_2O_7$ Required: C: 51.1% H; 4.1% N; 3.1%

(6.9% water)

Example 3

The following compounds may also be made by the processes described above:-

(i) 5-Ethyl-4,8-dioxo-10-propyl-4H,8H-pyrano[2,3-h]-quinoline-2,6-dicarboxylic acid

(ii) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-dicarboxylic acid

(iii) 10-Bromo-4,6-dioxo-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(iv) 5-Hydroxy-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

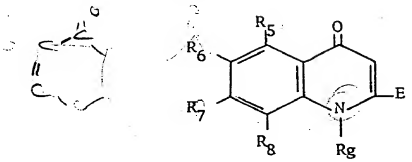
(v) 4,9-Dioxo-4H,9H-pyrano[2,3-g]quinoline-2,7-dicarboxylic acid

(vi) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-di[N-(tetrazol-5-yl)]carboxamide

(vii) 10-Bromo-4,6-dioxo-2,8-di-(tetrazol-5-yl)-4H,6H-pyrano[3,2-g]quinoline.

We claim: Amended "B"

1. A compound of formula I,



I

in which an adjacent pair of R_5, R_6, R_7 and R_8, form a chain -COCH=CE-O-, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and each of Rg, R_5, R_6, R_7, R_8, R_1 and R_2, when they ~~contain~~ have carbon, ~~containing~~ having up to 8 carbon atoms,

E is -COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable salts, and when E is a -COOH group, pharmaceutically acceptable esters and amides thereof.

2. A compound according to Claim 1, wherein each of Rg, R_5, R_6, R_7 and R_8 when they ~~contain~~ have carbon, ~~contain~~ have up to 4 carbon atoms.

3. A compound according to Claim 1, wherein the -COCH=CE-O- chain is bonded in positions R_6 and R_7, the -O- part of the chain being in position R_7.

4. A compound according to Claim 1, wherein R_5, R_6, R_7 and R_8 are

selected from hydrogen, methoxy, propyl, allyl, methyl, ethyl, chlorine, bromine and hydroxy.

5. A compound according to Claim 1, wherein E is a -COOH group.

6. A compound according to Claim 1 which is

4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid.

7. A compound according to Claim 1 which is

4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid,

5-Ethyl-4,8-dioxo-10-propyl-4H,8H-pyrano[2,3-h]quinoline-2,6-dicarboxylic acid,

4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-dicarboxylic acid,

10-Bromo-4,6-dioxo-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid,

5-Hydroxy-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid,

4,9-Dioxo-4H,9H-pyrano[2,3-g]quinoline-2,7-dicarboxylic acid,

4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-di[N-(tetrazol--5-yl)]-carboxamide, or

10-Bromo-4,6-dioxo-2,8-di-(tetrazol-5-yl)-4H,6H-pyrano-[3,2-g]quinoline.

8. The ethyl ester of a compound according to Claim 1.

9. The sodium salt of a compound according to Claim 1.

10. A pharmaceutical composition suitable for the treatment of a condition involving an antibody antigen reaction or a reflex pathway comprising an effective amount "A" of a compound according to Claim 17 in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A composition according to Claim 10 comprising less than 80% by weight of active ingredient.

12. A composition comprising from 0.01 mg to 50 mg of a compound according to Claim 17, as active ingredient, in unit dosage form.

13. A method of treatment of a condition involving an antibody antigen reaction or a reflex pathway, which comprises administering an effective amount of a compound according to Claim 17 to an animal suffering ~~or liable to suffer~~ from such a condition.

~~New Claims 14 - 16 added per~~ .

New claim 17, 18, 19, 20, 21, 22 + 23 added "A"

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Continuation Application U.S. Serial No. 946,492 Filed September 28, 1978	)	"COMPOUNDS"
HUGH CAIRNS ET AL.	)	Our File D-6181
Filed Herewith	)	

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

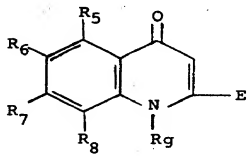
Sir:

Please amend the above-identified application as follows:

IN THE CLAIMS

Amend claim 1 as follows:

--1. (Amended) A compound of formula I,



I

in which an adjacent pair of R_5, R_6, R_7 and R_8, form a chain -COCH=CE-O-, and the remainder of R_5, R_6, R_7 and R_8, which may be the same or different, [each represent] are sterically compatible substituents selected from hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, [or] and $-NR_1R_2$ in which R_1 and R_2, which are the same or different, are each hydrogen or alkyl,

Rg is hydrogen, alkyl, alkenyl or phenyl-alkyl, and each of Rg, R_5, R_6, R_7, R_8, R_1 and R_2, when they [contain] have carbon, [containing] having up to 8 carbon atoms,

E is -COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable salts, and when E is a -COOH group, pharmaceutically acceptable esters selected from the ethyl ester, the β-(diethylamino)-ethyl ester, the pivaloyloxymethyl ester, and the bis-oxapropan-1,3-diyl ester, and pharmaceutically acceptable amides selected from unsubstituted amides and mono- or di- C_1 to C_6 alkyl amides thereof.--

Claim 2, line 2, cancel "contain", both occurrences, and insert in place thereof --have--.

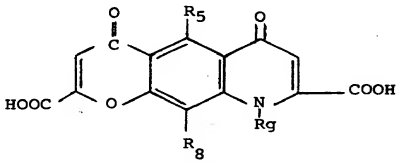
Claim 10, line 3, after "comprising", insert --an effective amount of--.

Claim 13, line 4, cancel "or liable to suffer".

Add the following claims:

Cancelled A

--14. A compound having the formula



wherein R_5 and R_8 are selected from hydrogen, methoxy, propyl, allyl, methyl, ethyl, chlorine, bromine and hydroxy,

and Rg is selected from hydrogen, alkyl, alkenyl or phenyl-alkyl, each of which, when it has carbon, has up to 8 carbon atoms.

Cancelled "A"

15. 4,6-dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid.

16. 4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid.--

REMARKS

The claims have been amended to conform to the amendments made during the prosecution of parent application Serial No. 946,492. New claims 14, 15 and 16 have been added, corresponding to the claims which were not entered in the parent application.

Respectfully submitted,

MERRIAM, MARSHALL & BICKNELL

By _____
Basil P. Mann (Reg. No. 18,464)
A Member of the Firm
Attorneys for Applicant
Two First National Plaza
Chicago, Illinois 60603
(312) 346-5750

Chicago, Illinois
January 28, 1982

DECLARATION COMBINED WITH PETITION AND POWER OF ATTORNEY
JOINT INVENTORS

ATTORNEY'S DOCKET NUMBER 5093

We, the undersigned petitioners, declare that the information in items 201, 202, and 301 below is true, that we believe that we are the original, first, and joint inventors of the invention described and claimed in the attached specification; that we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application; that, as to subject matter of this application which is common to our earlier United States application, if any, described in item 105 below, we do not believe that the same was ever known or used in the United States before our invention thereof or patented or described in any printed publication in any country before our invention thereof or more than one year prior to said earlier application, or in public use or on sale in the United States more than one year prior to said earlier application, that the said common subject matter has not been patented or made the subject of an inventor's certificate before the date of said earlier application in any country foreign to the United States on an application, filed by us or our legal representatives or assigns more than twelve months prior to said application and that no application for patent or inventor's certificate on said subject matter has been filed by us or our representatives or assigns in any country foreign to the United States except those identified in item 600 below, if any; that, as to any subject matter of this application which is not common to said earlier application, we do not know and do not believe that the same was ever known or used in the United States before our invention thereof or patented or described in any printed publication in any country before our invention thereof or more than one year prior to the date of this application, or in public use or on sale in the United States more than one year prior to the date of this application, and that said subject matter has not been patented or made the subject of an investor's certificate in any country foreign to the United States on an application filed by us or our legal representatives or assigns more than twelve months prior to the date of this application; and that no application for patent or inventor's certificate on said non-common subject matter has been filed by us or our representatives or assigns in any country foreign to the United States, except those identified in item 600 below.

201	FULL NAME OF APPLICANT (FIRST, MIDDLE, LAST) HUGH CAIRNS	CITIZENSHIP (COUNTRY) Great Britain
202	RESIDENCE CITY / STATE (OR FOREIGN COUNTRY) 2 Oxburgh Close, Thorpe Acre, Loughborough, Leicestershire, England	
201	FULL NAME OF APPLICANT (FIRST, MIDDLE, LAST) DAVID COX	CITIZENSHIP (COUNTRY) Great Britain
202	RESIDENCE CITY / STATE (OR FOREIGN COUNTRY) 60 Atherstone Road, Loughborough, Leicestershire, England	
201	FULL NAME OF APPLICANT (FIRST, MIDDLE, LAST)	CITIZENSHIP (COUNTRY)
202	RESIDENCE CITY / STATE (OR FOREIGN COUNTRY)	
201	FULL NAME OF APPLICANT (FIRST, MIDDLE, LAST)	CITIZENSHIP (COUNTRY)
202	RESIDENCE CITY / STATE (OR FOREIGN COUNTRY)	

301 TITLE OF INVENTION
COMPOUNDS

600 CHRONOLOGICAL LISTING OF FOREIGN APPLICATIONS, IF ANY, FILED WITHIN 12 MONTHS FROM THE DATE OF THIS APPLICATION.

COUNTRY	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 USC 119
Great Britain	45865/77	4th November 1977	☒ YES ☐ NO
Great Britain	16168/78	25th April 1978	☒ YES ☐ NO
			☐ YES ☐ NO

600 CHRONOLOGICAL LISTING OF FOREIGN APPLICATIONS, IF ANY, FILED MORE THAN 12 MONTHS PRIOR TO THIS APPLICATION.

COUNTRY	APPLICATION NUMBER	DATE OF FILING
Great Britain	16597/77	4th May 1977

CHECK APPROPRIATE BOX IF APPLICABLE: THIS APPLICATION IS A ☐ CONTINUATION ☐ DIVISION
☒ CONTINUATION-IN-PART (AS DESCRIBED IN THE ATTACHED SPECIFICATION ON PAGE 1) OF OUR PRIOR U.S. APPLICATION

105

SERIAL NUMBER	FILED
897 416	18th April 1978

WE HEREBY APPOINT THE FOLLOWING AS OUR ATTORNEY(S) OR AGENT(S) WITH FULL POWER OF SUBSTITUTION TO PROSECUTE THIS APPLICATION AND TRANSACT ALL BUSINESS IN THE PATENT OFFICE CONNECTED THEREWITH:

401

William E. Dominick (15,286)	Basil P. Mann (18,464)	Allen H. Gerstein (22,218)
Albert W. Bicknell (15,389)	Harry E. Burke (18,631)	Nate F. Scarpelli (22,320)
William A. Marshall (17,053)	Alvin D. Shulman (19,412)	Edward M. O'Toole (22,477)
Jerome B. Klose (17,104)	Donald J. Brott (19,490)	Michael F. Borun (25,447)
Norman M. Shapiro (17,812)	Owen J. Murray (22,111)	Carl E. Moore, Jr. (26,487)

SEND CORRESPONDENCE TO:

500

NAME	PHONE NO.	STREET	CITY & STATE	ZIPCODE
Merriam, Marshall & Bicknell	312—346-5750	Two First National Plaza Suite 2100	Chicago, Illinois	60603

Wherefore we petition that letters patent be granted to us for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe our names to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

HUGH CAIRNS

SIGNATURE OF APPLICANT — DATE

POST OFFICE ADDRESS OF APPLICANT

STREET ADDRESS	CITY	STATE OR COUNTRY	ZIPCODE
2 Oxburgh Close, Thorpe Acre,	Loughborough, Leicestershire, England		

DAVID COX

SIGNATURE OF APPLICANT — DATE

POST OFFICE ADDRESS OF APPLICANT

STREET ADDRESS	CITY	STATE OR COUNTRY	ZIPCODE
60 Atherstone Road,	Loughborough, Leicestershire, England		

Hugh Cairns

SIGNATURE OF APPLICANT — DATE 11 Sept 1978.

POST OFFICE ADDRESS OF APPLICANT

STREET ADDRESS	CITY	STATE OR COUNTRY	ZIPCODE

David Cox.

SIGNATURE OF APPLICANT — DATE 11 Sept 1978.

POST OFFICE ADDRESS OF APPLICANT

STREET ADDRESS	CITY	STATE OR COUNTRY	ZIPCODE

Rev. 5/75

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Case Docket No. 6181

Anticipated Classification
Class ____ Subclass ____

THE HON. COMMISSIONER OF PATENTS
AND TRADEMARKS,
Washington, D. C. 20231

Prior Application:
Examiner David B. Springer
Art Unit 122

Sir:

This is a request for filing a

[X] Continuation

[ ] Divisional

application under 37 CFR 1.60.

of pending prior application Serial No. 946,492 filed on September 28, 1978 (date) of HUGH CAIRNS ET AL. (inventor)

for "COMPOUNDS" (title of invention)

1. [ ] Enclosed is a copy of the prior application, including the oath or declaration as originally filed and an affidavit or declaration verifying it as a true copy.

2. [X] Prepare a copy of the prior application.

3. [X] The filing fee is calculated below:

Claims as Filed, Less Any Claims Cancelled by Amendment Below

For	Number Filed		Number Extra		Rate	Basic Fee $65.00
Total claims	13	-10 =	3	x	$ 2.00	$6.00
Independent claims	1	- 1 =	0	x	$10.00	$
			Total filing fee			$ 71.00

4. [X] The Commissioner is hereby authorized to charge any fees which may be required, or to credit any overpayment to Account No. 13-2855. A duplicate copy of this sheet is enclosed.

5. [X] A check in the amount of $ 71.00 is enclosed.

6. [ ] Cancel claims _____.

7. [X] Amend the specification by inserting before the first line the sentence: --This is a [X] continuation, [ ] division of application Serial No. 946,492, filed September 28, 1978.--

8. [ ] Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate of this sheet is enclosed for filing in the prior application file.

8a. [ ] New formal drawings, or [ ] informal drawings are enclosed.

8b. [X] Priority of application serial no. 48565/77; 16168/78; 18597/77 filed on 11/4/77; 4/25/78 and 5/4/77, in GREAT BRITAIN. is claimed under 35 U.S.C. 119.

[X] The certified copy(s) have been filed in prior application Serial No. 946,492, filed September 28, 1978.

9. [X] The prior application is assigned of record to FISONS LIMITED.

10. [X] The power of attorney in the prior application includes:

William E. Dominick (15,286)
Albert W. Bicknell (15,389
William A. Marshall (17,053)
Jerome B. Klose (17,104)
Norman M. Shapiro (17,812)
Basil P. Mann (18,464)
Harry E. Burke (18,631)
Alvin D. Shulman (19,412)
Donald J. Brott (19,490)
Owen J. Murray (22,111)
Allen H. Gerstein (22,218)
Nate F. Scarpelli (22,320)
Edward M. O'Toole (22,477)
Michael F. Borun (25,447)
Carl E. Moore, Jr. (26,487)

(a) [X] The power appears in the original papers of the prior application.

(b) [ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

(c) [X] Address all future communications to Basil P. Mann (Reg. No. 18,464) MERRIAM, MARSHALL & BICKNELL Two First National Plaza Chicago, Illinois 60603 (name, Reg. No., and Address)

11. [X] A preliminary amendment is enclosed.

Basil P. Mann

(signature)

Basil P. Mann (Reg. No. 18,464)
Attorney or agent of record in prior application.

U.S. DEPARTMENT OF COMMERCE
Patent Office

Address Only: COMMISSIONER OF PATENTS
Washington, D.C. 20231

In re application of Continuation of U.S. Serial No. 946,492

Serial No.

Filed Herewith

For "COMPOUNDS"

THE COMMISSIONER OF PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is enclosed because this application was filed prior to October 25, 1965 (effective date of Public Law 89-83.)

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
	(2) CLAIMS REMAINING AFTER AMENDMENT		(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	* 16	MINUS	** 13	x 3	x $2	x 6.00
INDEP. CLAIMS	* 4	MINUS	1	x 3	x $10	x 30.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT →			36.00

*If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
**If the "Highest Number Previously Paid For" IN THIS SPACE is less than 10, write "10" in this space.

☒ A check in the amount of $36.00 is attached.

☐ Charge $ to Deposit Account No. _____. A duplicate copy of this sheet is enclosed.

☒ Please charge any additional fees or credit overpayment to Deposit Account No. 13-2855. A duplicate copy of this sheet is enclosed.

MERRIAM, MARSHALL & BICKNELL

Basil P. Mann

Basil P. Mann (Reg. No. 18,464)
Attorney of Record
Two First National Plaza, Suite 2100
Chicago, Illinois 60603
(312) 346-5750

Dated: January 28, 1982

FORM PO-1083 (11-69)

USCOMM-DC 60425-P69

THE COMPANIES ACT 1985

Company No. 44687

The Registrar of Companies for England and Wales hereby certifies that FISONS plc (originally called EDWARD PACKARD & CO., LIMITED, which name was changed on 27th August 1920 to PACKARDS, AND FISONS (THETFORD) LIMITED, which name was changed on 16th November 1920 to PACKARDS, AND JAMES FISON (THETFORD) LIMITED, which name was changed on 7th August 1929 to FISON, PACKARD & PRENTICE, LIMITED, which name was changed on 30th September 1942 to FISONS LIMITED, each change having been made by special resolution and with the approval of the Board of Trade) was incorporated under the Companies Acts 1862 to 1890 as a limited company on 23rd July 1895 and re-registered under the Companies Acts 1948 to 1980 as a public company on 1st March 1982.

The Registrar further certifies that according to the latest notice given by the company, the situation of the registered office is FISON HOUSE, PRINCES STREET, IPSWICH, IP1 1QH.

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Given at Companies House, Cardiff, the 15th November 1991

MISS. A. ODHAM
for the Registrar of Companies

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: Application for extension of patent term under 35 U.S.C. §156

Patent No: 4,474,787, issued October 2, 1984

Applicant: Fisons plc (formerly Fisons Limited)
Fison House
Princes Street
Ipswich
Suffolk IP1 1QH
England

Power of Attorney

The undersigned applicant hereby appoints

Basil P. Mann (Reg No: 18,464)
Marshall, O'Toole, Gerstein, Murray & Bicknell
Two First National Plaza
Suite 2100
Chicago, Illinois 60603
(312) 346-5750

as its attorney to execute the above-identified application to extend the term of US Patent No: 4,474,787 on its behalf, and to transact all business in the Patent and Trademark Office connected therewith.

Fisons plc

By C A Scroggs
Chief Executive

Date 19th Feb 1993